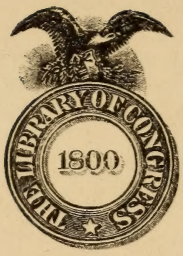

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THE CHEMISTRY AND ANALYSIS OF DRUGS AND MEDICINES

BY

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INTRODUCTION

WHOEVER has taken up an investigation of drugs and medicines, whether in the line of analysis or research, must have been impressed with the fact that there has been no individual publication dealing with analytical procedures applicable to the subject as a whole.

The analyst could turn to the Pharmacopœia and National Formulary for methods of assaying and testing the official drugs, and to other works such as Autenreith and Warren's "Detection of Poisons," "New and Non-Official Remedies" published by the American Medical Association, and the publications of the Association of Official Agricultural Chemists, where he would find information and perhaps methods applicable to certain classes of drugs and medicinal agents, but there has been no general analytical work embracing this branch of chemistry. The food analyst could turn to Leach's "Food Inspection and Analysis," and there find complete the latest methods for solving his analytical problems, but the drug analyst was less fortunate, and when presented with a problem of analysis outside the usual run of drug assaying, there was involved a long search through the available text books, technical journals, and official publications before a satisfactory procedure was found, if any existed.

The work in hand has been published in order to remedy this situation.

The material for it has been collected during the past seventeen years, and has been arranged in a way which it is believed will be found convenient to the worker who is handling miscellaneous analytical investigations.

Problems of analysis of drugs and medicines are many and varied. Those most frequently met with may be grouped as follows:

The assaying of individual crude drugs and medicinal chemicals;

The analysis of mixtures for one or more essential ingredients;

The determination of the character and amounts of the components of a medicine, either for purposes of duplication, or for the basis of a court proceeding;

The testing of individual substances for their identity and purity;

The separation and identification of the hitherto unknown constituents of crude drugs;

The identification of small quantities of toxic principles.

The subject matter in this work has been arranged in general in accordance with its chemical relationship, although in that portion dealing with organic substances the sequence in which one group follows another in theoretical chemistry has not been followed. In the groups themselves some substances have been discussed simultaneously with those with which they are medicinally allied, even though they may not be related to them chemically. For instance, it is obviously more comprehensive to include all of the local anesthetics under the chapter on "Cocain" than to scatter them through the various groups of organic compounds under which they would fall because of their chemical relationship.

By far the larger proportion of the number of the individual drugs and remedial agents belong to the class of organic substances. In the general arrangement the natural drugs and their derivatives have been considered first, then follows the individual organic substances, including most of the so-called "synthetics," and lastly the inorganic drugs.

Those characteristics of the different substances valuable for their analytical significance have been detailed, many new, important and hitherto obscure reactions have been recorded, and wherever reliable quantitative methods of determination and separation could be found, they have been described.

In the treatment of the individual drugs and medicinal agents considerable space has been devoted to detailing the character of the remedies in which they commonly occur, and the combinations usually found in practice. Knowledge of this kind is of great aid to the analyst, and will often save a vast amount of unnecessary labor when he is working with an unknown mixture. As a matter of fact, if the analyst has at his disposal the latest catalogues of the large pharmaceutical houses, he will often obtain valuable assistance in arriving at the probable composition of a remedy, once he knows for what purpose it is to be used, and the identity of one or more of the essential ingredients.

A section of the work has been devoted to some general determinations which are often necessary in analyzing galenicals, and for the convenience of the drug assayist a section has been given over to drug assays in which are assembled all of the reliable representative methods available for analyzing crude drugs.

In the various groups, especially in the organic section, references will be found to many substances which are not used medicinally, but which, by reason of their properties, are closely related to those having direct connection with the general subject. These individuals have been noted because it often happens, especially when working up a court case, that the chemist finds it necessary to refresh his knowledge concerning the members of a given series of organic substances other than the particular one which will figure in the case.

No attempt has been made in general to go into the description of the botanical drugs from the standpoint of the pharmacognosist. To have consumed space with their descriptions would only have duplicated such special works on the subject, as Kraemer's "Botany and Pharmacognosy."

Data for this work have been drawn freely from authorities who have handled special subjects, and in each instance due reference and credit have been given. Much material has appeared in the literature during the past twenty years; practically all of this has been reviewed, and that which was reliable and essential has been quoted. The assembling and classification of all this material, and the testing out of the methods, have involved considerable research, but it is believed that the object in view justified the endeavor, and that there has been evolved a work which will be greatly appreciated by those concerned with the inspection and analysis of drugs and medicines.

Part I

GENERAL METHODS AND CRUDE DRUG ASSAYS

CHAPTER I

GENERAL METHODS

It is almost a waste of time to begin the quantitative analysis of a medicinal product until one has determined by carefully performed qualitative investigation the nature of the substances present. In food analysis one can often determine the percentages of moisture, ash, nitrogen, starch, rotatory power before and after inversion, the presence or absence of preservatives and then interpret his results. Not so with drug analysis. Except in cases where the worker has to deal with extracts or substances containing but one ingredient, each preparation offers a problem by itself and often a dozen samples containing the same single ingredient, put out by a dozen different firms, will require different procedures owing to the difference in pharmaceutical make up.

There are, however, certain general tests which must be applied to large groups of substances regardless of their composition, and for convenience they have been detailed at this point.

In the cases of all liquid preparations, the specific gravity and alcohol should be estimated; in both liquids and solid medicinal agents the total non-volatile matter, ash, and sugar determined as a guide and check in arriving at the final composition, and the presence and amount of arsenic should be established.

SPECIFIC GRAVITY

This datum should be determined with an accurate pycnometer at a convenient temperature, such as 15.6° or 20° C. The result is an aid in the future determinations and obviates the weighing out of the sample if the measurements are made in accurately graduated flasks or pipettes.

ALCOHOL

If the sample contains but negligible quantities of volatile matter other than alcohol and water, the alcohol may be estimated by simple distillation and determining the amount from the specific gravity of the distillate, which should be so regulated that it does not contain over 50 per cent of alcohol and for satisfactory results never more than 35 per cent, hence if the sample is suspected of containing over 50 per cent alcohol, it should be distilled and made up to twice its original volume.

If the sample is acid and contains no free iodine, it sould be neutralized with alkali and the distillate should be subsequently tested with litmus to determine its alkalinity. In certain instances, when ammonium salts occur in mixtures containing alkaloids or alkaloid-bearing drugs, free ammonia will be disengaged, and the distillate must be neutralized with sulphuric or phosphoric acid and again distilled.

If iodine be present, it can be fixed with sodium thiosulphate.

The determination is made by filling to the mark an accurately graduated 50-mil flask, observing the proper temperature at which the flask is graduated, and pouring the contents into the retort flask of a distilling apparatus; the flask is washed out with three portions of 15 to 20 mils of distilled water, pouring the water into the flask of the distilling apparatus. Distillation is then conducted into the flask in which the original measurement was made or one of double its capacity, having it surrounded with ice water, until it is about three-quarters full, when it is removed and made up with distilled water to volume, the temperature being adjusted to that at which the original measurement was made. The specific gravity is determined at 15.6° or 20° C. by means of an accurate pycnometer, and from the figure obtained the alcoholic percentage determined from the standard table.

When working with sarsaparilla, soapwort, or other solutions containing saponin-like bodies which produce frothing, a small amount of paraffin or petrolatum should be added to prevent the liquid from bubbling over into the receiver. With some mixtures it may prove more satisfactory to distill without attempting to prevent some of the bubbles from going over and then to conduct a second distillation.

The presence of g ycerin has no effect on the accuracy of the method, for this substance does not come over with the distillate unless the concentration of the glycerin solution is over 70 per cent. Acetanilid will distill in small amounts, but its presence in the distillate does not affect the accuracy of the method.

If volatile oils, chloroform, ether, camphor, or like substances are present, the method must be modified by the principle advanced by Thorpe and Holmes[1] using petroleum ether and sodium chloride to salt

[1] J. Chem. Soc., 1903, 83, 313.

ALCOHOLOMETRIC TABLE

Temperature 15.56° C.

Percentage by Volume					Percentage by Weight				
Per Cent Vol.	Corresponding Per Cent Weight	Sp. Gr. App.* in Air $\frac{15.56°}{15.56°}$	Corr.† of Sp. Gr. for Barometer (100 mm.)	Fractional‡ Per Cent	Per Cent Wt.	Corresponding Per Cent Volume	Sp. Gr. App.* in Air $\frac{15.56°}{15.56°}$	Corr.† of Sp. Gr. for Barometer (100 mm.)	Fractional‡ Per Cent
§0	0.000	1.00000	0.000000	0.0667	0	0.000	1.00000	0.000000	0.0532
1	0.795	0.99850	0.000000	0.0680	1	1.257	0.99812	0.000000	0.0543
2	1.593	0.99703	0.000000	0.0690	2	2.510	0.99628	0.000000	0.0565
3	2.392	0.99558	0.000001	0.0714	3	3.758	0.99451	0.000001	0.0588
4	3.194	0.99418	0.000001	0.0730	4	5.002	0.99281	0.000001	0.0610
5	3.998	0.99281	0.000001	0.0746	5	6.243	0.99117	0.000001	0.0641
6	4.804	0.99149	0.000001	0.0781	6	7.479	0.98961	0.000001	0.0671
7	5.612	0.99021	0.000001	0.0813	7	8.712	0.98812	0.000002	0.0680
8	6.422	0.98898	0.000002	0.0833	8	9.943	0.98665	0.000002	0.0700
9	7.234	0.98778	0.000002	0.0840	9	11.169	0.98523	0.000002	0.0719
10	8.047	0.98659	0.000002	0.0855	10	12.393	0.98384	0.000002	0.0746
11	8.862	0.98542	0.000002	0.0877	11	13.613	0.98351	0.000003	0.0769
12	9.679	0.98428	0.000002	0.0901	12	14.832	0.98120	0.000003	0.0775
13	10.497	0.98317	0.000003	0.0917	13	16.047	0.97991	0.000003	0.0800
14	11.317	0.98208	0.000003	0.0943	14	17.259	0 97866	0.000003	0.0820
15	12.138	0.98102	0.000003	0.0943	15	18.469	0.97744	0.000004	0.0840
16	12.961	0.97996	0.000003	0.0962	16	19.676	0.97625	0.000004	0.0833
17	13.786	0.97892	0.000003	0.0990	17	20.880	0.97505	0.000004	0.0826
18	14.612	0.97791	0.000004	0.1000	18	22.081	0.97384	0.000004	0.0813
19	15.440	0.97691	0.000004	0.1020	19	23.278	0.97261	0.000004	0.0806
20	16.269	0.97593	0.000004	0.1000	20	24.472	0.97137	0.000005	0.0794
21	17.100	0.97493	0.000004	0.0990	21	25.662	0.97011	0.000005	0.0781
22	17.933	0.97392	0.000004	0.0980	22	26.849	0.96883	0.000005	0.0769
23	18.768	0.97290	0.000004	0.0962	23	28.032	0.96753	0.000005	0.0752
24	19.604	0.97186	0.000005	0.0952	24	29.210	0.96620	0.000005	0.0740
25	20.443	0.97081	0.000005	0.0943	25	30.388	0.96485	0.000006	0.0719
26	21.285	0.96974	0.000005	0.0926	26	31.555	0.96346	0.000006	0.0694
27	22.127	0.96866	0.000005	0.0909	27	32.719	0.96202	0.000006	0.0667
28	22.973	0.96756	0.000005	0.0893	28	33.879	0.96052	0.000006	0.0649
29	23.820	0.96644	0.000005	0.0877	29	35.033	0.95898	0.000007	0.0633
30	24.670	0.96530	0.000005	0.0862	30	36.181	0.95740	0.000007	0.0613

ALCOHOLOMETRIC TABLE—*Continued*

Percentage by Volume					Percentage by Weight				
Per Cent Vol.	Corresponding Per Cent Weight	Sp. Gr. App.* in Air $\frac{15.56°}{15.56°}$	Corr.† of Sp. Gr. for Barometer (100 mm.)	Fractional‡ Per Cent	Per Cent Wt.	Corresponding Per Cent Volume	Sp. Gr. App.* in Air $\frac{15.56°}{15.56°}$	Corr.† of Sp. Gr. for Barometer (100 mm.)	Fractional‡ Per Cent
31	25.524	0.96414	0.000006	0.0820	31	37.323	0.95577	0.000007	0.0595
32	26.382	0.96292	0.000006	0.0787	32	38.459	0.95409	0.000007	0.0578
33	27.242	0.96165	0.000006	0.0775	33	39.590	0.95236	0.000007	0.0565
34	28.104	0.96036	0.000006	0.0752	34	40.716	0.95059	0 000008	0.0556
35	28.971	0.95903	0.000006	0.0725	35	41.832	0.94879	0.000008	0.0546
36	29.842	0.95765	0.000007	0.0704	36	42.944	0.94696	0.000008	0.0538
37	30.717	0.95623	0.000007	0.0685	37	44.050	0.94509	0.000009	0.0521
38	31.596	0.95477	0.000007	0.0668	38	45.149	0.94317	0.000009	0.0515
39	32.478	0.95326	0.000007	0.0649	39	46.242	0.94123	0.000009	0.0508
40	33.364	0.95172	0.000007	0.0633	40	47.328	0.93926	0.000010	0.0498
41	34.254	0.95014	0.000008	0.0617	41	48.407	0.93725	0.000010	0.0488
42	35.150	0.94852	0.000008	0.0600	42	49.480	0.93520	0.000010	0.0485
43	36.050	0.94687	0.000008	0.0588	43	50.545	0.93312	0.000011	0.0476
44	36.955	0.94517	0.000009	0.0578	44	51.605	0.93102	0.000011	0.0474
45	37.865	0.94344	0.000009	0.0565	45	52.658	0.92891	0.000011	0.0469
46	38.778	0.94167	0.000009	0.0552	46	53.705	0.92678	0.000012	0.0467
47	39.697	0.93986	0.000009	0.0541	47	54.746	0.92464	0.000012	0.0461
48	40.622	0.93801	0.000010	0.0526	48	55.780	0.92247	0.000012	0.0461
49	41.551	0.93611	0.000010	0.0518	49	56.808	0.92030	0.000013	0.0457
50	42.487	0.93418	0.000010	0.0510	50	57.830	0.91811	0.000013	0.0455
51	43.428	0.93222	0.000011	0.0503	51	58.844	0.91591	0.000013	0.0446
52	44.374	0.93023	0.000011	0.0498	52	59.851	0.91367	0.000014	0.0444
53	45.326	0.92822	0.000011	0.0488	53	60.854	0.91142	0.000014	0.0444
54	46.283	0.92617	0.000012	0.0483	54	61.850	0.90917	0.000014	0.0442
55	47.245	0.92410	0.000012	0.0478	55	62.837	0.90691	0.000015	0.0441
56	48.214	0.92201	0.000012	0.0474	56	63.820	0.90464	0.000015	0.0441
57	49.187	0.91990	0.000013	0.0463	57	64.798	0.90237	0.000015	0.0441
58	50.167	0.91774	0.000013	0.0457	58	65.768	0.90010	0.000016	0.0437
59	51.154	0.91555	0.000013	0.0452	59	66.732	0.89781	0.000016	0.0435
60	52.147	0.91334	0.000014	0.0446	60	67.690	0.89551	0.000016	0.0433
61	53.146	0.91110	0.000014	0.0439	61	68.641	0.89320	0.000017	0.0431
62	54.152	0.90882	0.000014	0.0437	62	69.586	0.89088	0.000017	0.0431
63	55.165	0.90653	0.000015	0.0435	63	70.523	0.88856	0.000017	0.0427
64	56.184	0.90423	0.000015	0.0429	64	71.455	0.88623	0.000018	0.0426
65	57.208	0.90190	0.000015	0.0426	65	72.380	0.88388	0.000018	0.0426

ALCOHOLOMETRIC TABLE—*Continued*

Percentage by Volume					Percentage by Weight				
Per Cent Vol.	Corresponding Per Cent Weight	Sp. Gr. App.* in Air $\frac{15.56°}{15.56°}$	Corr.† of Sp. Gr. for Barometer (100 mm.)	Fractional‡ Per Cent	Per Cent Wt.	Corresponding Per Cent Volume	Sp. Gr. App.* in Air $\frac{15.56°}{15.56°}$	Corr.† of Sp. Gr. for Barometer (100 mm.	Fractional‡ Per Cent
66	58.241	0.89955	0.000016	0.0420	66	73.299	0.88153	0.000019	0.0426
67	59.279	0.89717	0.000016	0.0410	67	74.211	0.87918	0.000019	0.0426
68	60.325	0.89477	0.000016	0.0408	68	75.117	0.87683	0.000019	0.0422
69	61.379	0.89232	0.000017	0.0407	69	76.016	0.87446	0.000020	0.0422
70	62.441	0.88986	0.000017	0.0403	70	76.909	0.87206	0.000020	0.0418
71	63.511	0.88738	0.000018	0.0395	71	77.794	0.86970	0.000021	0.0417
72	64.588	0.88485	0.000018	0.0392	72	78.672	0.86730	0.000021	0.0417
73	65.674	0.88230	0.000019	0.0389	73	79.544	0.86490	0.000021	0.0417
74	66.768	0.87973	0.000019	0.0385	74	80.410	0.86250	0.000022	0.0413
75	67.870	0.87713	0.000019	0.0380	75	81.269	0.86008	0.000022	0.0413
76	68.982	0.87450	0.000020	0.0376	76	82.121	0.85766	0.000022	0.0413
77	70.102	0.87184	0.000020	0.0370	77	82.967	0.85524	0.000023	0.0412
78	71.234	0.86914	0.000021	0.0365	78	83.805	0.85281	0.000023	0.0403
79	72.375	0.86640	0.000021	0.0362	79	84.636	0.85033	0.000024	0.0408
80	73.526	0.86364	0.000021	0.0357	80	85.459	0.84788	0.000024	0.0403
81	74.686	0.86084	0.000022	0.0352	81	86.275	0.84540	0.000024	0.0402
82	75.858	0.85800	0.000022	0.0350	82	87.083	0.84291	0.000025	0.0402
83	77.039	0.85514	0.000023	0.0344	83	87.885	0.84042	0.000025	0.0398
84	78.233	0.85223	0.000023	0.0337	84	88.678	0.83791	0.000025	0.0394
85	79.441	0.84926	0.000024	0.0331	85	89.464	0.83537	0.000026	0.0392
86	80.662	0.84624	0.000024	0.0326	86	90.240	0.83282	0.000026	0.0391
87	81.897	0.84317	0.000025	0.0322	87	91.008	0.83026	0.000027	0.0386
88	83.144	0.84006	0.000025	0.0314	88	91.766	0.82767	0.000027	0.0377
89	84.408	0.83688	0.000026	0.0307	89	92.517	0.82502	0.000028	0.0380
90	85.689	0.83362	0.000026	0.0300	90	93.254	0.82239	0.000028	0.0372
91	86.989	0.83029	0.000027	0.0291	91	93.982	0.81970	0.000028	0.0367
92	88.310	0.82685	0.000027	0.0282	92	94.700	0.81697	0.000029	0.0362
93	89.652	0.82330	0.000028	0.0272	93	95.407	0.81421	0.000029	0.0358
94	91.025	0.81963	0.000028	0.0262	94	96.103	0.81142	0.000030	0.0353
95	92.423	0.81581	0.000029	0.0252	95	96.787	0.80859	0.000030	0.0348
96	93.851	0.81184	0.000030	0.0240	96	97.457	0.80572	0.000030	0.0342
97	95.315	0.80769	0.000030	0.0229	97	98.117	0.80280	0.000031	0.0334
98	96.820	0.80333	0.000031	0.0214	98	98.759	0.79981	0.000031	0.0328
99	98.381	0.79865	0.000031	0.0200	99	99.386	0.79676	0.000032	0.0322
100	100.000	0.79365	0.000032		100	100.000	0.79365	0.000032	

out the volatile ingredients. Unless the mixture contains considerable fixed residue such as mineral salts, sugar, or drug extractive, the procedure can be carried out on the original sample, but if these are present in marked quantity a preliminary distillation should be made. Then the solution is transferred to a separator, diluted with water if necessary until the alcoholic content is not over 25 per cent, excess of solid sodium chloride added, and shaken out three times with about one-fourth its volume of low-boiling petroleum ether. The petroleum ether washings are collected in another separator, washed with saturated salt solution, the latter added to the main liquid and the whole distilled.

NON-VOLATILE MATERIAL AND ASH

The non-volatile material can often be determined in the residue remaining in the distilling flask from the alcohol determination unless it was necessary to manipulate the solution in some way before carrying out the distillation. In case this is not feasible 10-25 mils of the original sample are used for the determination, measurement being made with an accurate pipette or graduated flask, the sample washed into a small porcelain dish and evaporated over the steam bath until there is apparently no further diminution in volume, and then transferred to a drying oven and exposed to the heat of 100° C. for five hours. The dish should be cooled in a desiccator and weighed rapidly, no attempt being made to go beyond the third decimal, as most of these residues are hygroscopic. This method will give one an idea of the amount of non-volatile material present. The water will be practically all eliminated in this time, and while continued heating will cause a further loss in weight, it is due to the expulsion of other volatile substances, the breaking down of sugar, the gradual volatilization of glycerin, etc. In the case of some mixtures the determination of non-volatile material by this method will prove of little value; for instance, if one is dealing with a headache mixture containing acetanilid, the latter will volatilize. Such preparations, after the water is nearly all driven off on the steam bath, should be allowed to dry for ten or twelve hours in a vacuum desiccator over sulphuric acid or calcium chloride.

ASH

After weighing the residue in the above determination, it should be carefully burned and the ash weighed, the result giving an approximate value of the quantity of mineral salts. If the ash is heavily impregnated with resistant carbon it can be leached with dilute acetic acid, the solution filtered, evaporated, and the filter paper and carbon returned to the dish and the whole burned a second time.

SUGAR

Sucrose or cane sugar enters into the composition of a large variety of medicinal substances, including elixirs, wines, syrups, cordials, pills, tablets, lozenges, pastilles, granular preparations and some powders. Lactose or milk sugar occurs in powders. Honey is often used. Commercial glucose is present in pill and tablet mixtures and to some extent probably in liquid preparations. Invert sugar will be present to some extent where sucrose has been hydrolyzed by acid. True glucose as a decomposition product of glucosides, as well as other less common sugars from the same sources will be found. The analyst will be chiefly concerned with determining the sugar which is present as one of the chief bulk ingredients.

The polariscopic methods for the estimation of sugar may be employed in the case of those mixtures which are free from caramel or contain substances which are readily removed by lead acetate, and by checking the determination by a copper reduction before and after inversion the amount can be obtained with a satisfactory degree of accuracy. This qualification must be made because there are many substances other than sugar which will affect the polarization and copper reduction to a greater or less extent, and their presence will, of course, have been established by a previous qualitative examination.

Sucrose [1]

Dissolve the normal weight (26 grams) of the substance in water, add basic lead acetate carefully, avoiding any excess, then 1-2 mils of alumina cream, shake, and dilute to 100 mils, filter, rejecting the first 20 mils of the filtrate, cover the filter with a watch glass and, when sufficient filtrate is collected, polarize in a 200-mm. tube. The reading so obtained is the direct reading (P of formula given below) or polarization before inversion. For the invert reading, remove the lead from the solution either (1) by adding anhydrous potassium oxalate, a little at a time, to the remaining solution, avoiding an excess and removing the precipitated lead by filtration; or, (2) by adding anhydrous sodium carbonate under the same conditions. Introduce 50 mils of the lead-free filtrate into a 100-mil flask (if sodium carbonate was used for removing the lead, neutralize carefully the excess of sodium carbonate with a few drops of dilute hydrochloric acid) and add 25 mils of water. Then add, little by little, while rotating the flask, 5 mils of hydrochloric acid (sp. gr. 1.20). Heat the flask after mixing, in a water-bath kept at 70° C. in $2\frac{1}{2}$ to 3 minutes. Maintain a temperature of as nearly 69° C. as possible for 7 to $7\frac{1}{2}$ minutes, making the total time of heating ten minutes. Remove the flask and cool the contents rapidly to 20° C. and dilute to 100 mils.

[1] By Polarization before and after Inversion with Hydrochloric Acid.—A.O.A.C.

Polarize this solution in a tube provided with a lateral branch and a water jacket, maintaining a temperature of 20° C. . This reading must be multiplied by 2 to obtain the invert reading. If it is necessary to work at a temperature other than 20° C., which is allowable within narrow limits, the volumes must be completed and both direct and invert polarizations must be made at exactly the same temperature.

The inversion may also be accomplished as follows: (1) To 50 mils of the clarified solution, freed from lead, add 5 mils of hydrochloric acid (sp. gr. 1.20) and set aside for twenty-four hours at a temperature not below 20° C.; or, (2) if the temperature be above 25° C. set aside for ten hours. Make up to 100 mils at 20° C. and polarize as directed above.

Calculate sucrose by one of the following formulas:

For Substances in which the Invert Solution Contains more than 12 Grams of Invert Sugar per 100 Mils.—The following formula is to be used when substances like raw sugars are polarized:

$$S = \frac{100\ (P-I)}{142.66 - \frac{T}{2}}$$

in which

S = per cent of sucrose;
P = direct reading normal solution;
I = invert reading normal solution;
T = temperature at which readings are made.

For Substances in which the Concentration of the Invert Solution is Less than 12 Grams per 100 Mils.—The following formula, which takes into account the concentration of the sugar in solution, should be used in all other cases.

$$S = \frac{100\ (P=I)}{142.66 = \frac{T}{2} = 0.0065(142.66 = \frac{T}{2} = (P=I))}$$

in which

S = per cent of sucrose;
P = direct reading normal solution;
I = invert reading normal solution;
T = temperature.

TOTAL SUGARS AND SUCROSE BY COPPER REDUCTION

For the copper reduction, the procedure of Munson and Walker gives the greatest satisfaction. The reagents consist of copper sulphate 34.6 grams to 500 mils; and alkaline tartrate, 173 grams Rochelle Salts, and 50 grams sodium hydrate to 500 mils. A determination should be made on the sample directly, then the amount given by inversion ascertained,

and from the figures the amount due to sucrose may be calculated. The quantity of the sample to be taken cannot be stated by any hard-and-fast rule, and the worker should make a few preliminary tests before running the actual determination. For liquids 10 to 25 mils will be sufficient, and for solids 10 grams will usually suffice.

After the sample has been accurately measured or weighed, it is introduced into a 100-mil graduated flask, diluted with water, precipitated with an excess of *neutral* lead acetate and made up to volume. A 25-mil aliquot is then precipitated with potassium oxalate, diluted to a definite volume without filtering, and the reducing sugars determined in a small portion of the clear liquid. Tenmils, or a sufficient quantity of this diluted solution are measured out with a pipette or burette and added to a mixture of 25 mils each of the copper and tartrate solution in a 400-mil beaker, 40 mils of water are added, the mixture brought to a boil as rapidly as possible, and boiled for two minutes. The cuprous oxide is then filtered onto an asbestos felt in a porcelain Gooch crucible, using suction, washed with warm water, dried with alcohol and ether, placed in an oven at 100° C. for half an hour and then cooled and weighed. For the sucrose determination a 50-mil aliquot of the original 100-mil solution of the sample is precipitated with potassium oxalate, filtered and a 25-mil portion of the filtrate inverted with hydrochloric acid as directed under "Sucrose" This liquid is then made up to volume and the total reduction determined.

The number of milligrams of copper reduced by a given amount of sugar differs when sucrose is present and when it is absent. In the sugar table there are two columns, one for a mixture of invert sugar and sucrose in the case of about .4 gram total sugar and another in case of about 2 grams; in addition there is a column for invert sugar alone.

The factor for sucrose is 0.95.

As has been stated above, there are a number of substances other than the well-known reducing sugars which throw out cuprous oxide from an alkaline copper solution, and for the benefit of the worker the following list has been compiled. It includes most of the individuals with which the worker will meet.

Acetaldehyde and all other aldehydes of the acetic series.

Arabinose	Gallotannic acid	Mannitose
Arsenous acid	Glycosuric acid	Pectinose
Chloral	Glycuronic acid	Pyrogallic acid
Chloroform	Glycyrrhizin	Resorcinol
Dextrose	Iso-dulcite	Rhamnose
Eucalyptose	Lactose	Sorbinose
Formaldehyde	Levulose	Trichlor acetic acid
Formic acid	Maltose	Zylose
Galactose		

MUNSON AND WALKER'S TABLE

For calculating dextrose, invert sugar alone, invert sugar in the presence of sucrose (0.4 gram and 2 grams total sugar), lactose (two forms), and maltose (anhydrous and crystallized).

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
10	8.9	4.0	4.5	1.6	.....	3.8	4.0	5.9	6.2	10
11	9.8	4.5	5.0	2.1	.....	4.5	4.7	6.7	7.0	11
12	10.7	4.9	5.4	2.5	.....	5.1	5.4	7.5	7.9	12
13	11.5	5.3	5.8	3.0	.....	5.8	6.1	8.3	8.7	13
14	12.4	5.7	6.3	3.4	.....	6.4	6.8	9.1	9.5	14
15	13.3	6.2	6.7	3.9	.....	7.1	7.5	9.9	10.4	15
16	14.2	6.6	7.2	4.3	.....	7.8	8.2	10.6	11.2	16
17	15.1	7.0	7.6	4.8	.....	8.4	8.9	11.4	12.0	17
18	16.0	7.5	8.1	5.2	.....	9.1	9.5	12.2	12.9	18
19	16.9	7.9	8.5	5.7	.....	9.7	10.2	13.0	13.7	19
20	17.8	8.3	8.9	6.1	.....	10.4	10.9	13.8	14.6	20
21	18.7	8.7	9.4	6.6	.....	11.0	11.6	14.6	15.4	21
22	19.5	9.2	9.8	7.0	.....	11.7	12.3	15.4	16.2	22
23	20.4	9.6	10.3	7.5	.....	12.3	13.0	16.2	17.1	23
24	21.3	10.0	10.7	7.9	.....	13.0	13.7	17.0	17.9	24
25	22.2	10.5	11.2	8.4	.....	13.7	14.4	17.8	18.7	25
26	23.1	10.9	11.6	8.8	.....	14.3	15.1	18.6	19.6	26
27	24.0	11.3	12.0	9.3	.....	15.0	15.8	19.4	20.4	27
28	24.9	11.8	12.5	9.7	.....	15.6	16.5	20.2	21.2	28
29	25.8	12.2	12.9	10.2	.....	16.3	17.1	21.0	22.1	29
30	26.6	12.6	13.4	10.7	4.3	16.9	17.8	21.8	22.9	30
31	27.5	13.1	13.8	11.1	4.7	17.6	18.5	22.6	23.7	31
32	28.4	13.5	14.3	11.6	5.2	18.3	19.2	23.3	24.6	32
33	29.3	13.9	14.7	12.0	5.6	18.9	19.9	24.1	25.4	33
34	30.2	14.3	15.2	12.5	6.1	19.6	20.6	24.9	26.2	34
35	31.1	14.8	15.6	12.9	6.5	20.2	21.3	25.7	27.1	35
36	32.0	15.2	16.1	13.4	7.0	20.9	22.0	26.5	27.9	36
37	32.9	15.6	16.5	13.8	7.4	21.5	22.7	27.3	28.7	37
38	33.8	16.1	16.9	14.3	7.9	22.2	23.4	28.1	29.6	38
39	34.6	16.5	17.4	14.7	8.4	22.8	24.1	28.9	30.4	39
40	35.5	16.9	17.8	15.2	8.8	23.5	24.8	29.7	31.3	40
41	36.4	17.4	18.3	15.6	9.3	24.2	25.4	30.5	32.1	41
42	37.3	17.8	18.7	16.1	9.7	24.8	26.1	31.3	32.9	42
43	38.2	18.2	19.2	16.6	10.2	25.5	26.8	32.1	33.8	43
44	39.1	18.7	19.6	17.0	10.7	26.1	27.5	32.9	34.6	44
45	40.0	19.1	20.1	17.5	11.1	26.8	28.2	33.7	35.4	45
46	40.9	19.6	20.5	17.9	11.6	27.4	28.9	34.4	36.3	46
47	41.7	20.0	21.0	18.4	12.0	28.1	29.6	35.2	37.1	47
48	42.6	20.4	21.4	18.8	12.5	28.7	30.3	36.0	37.9	48
49	43.5	20.9	21.9	19.3	12.9	29.4	31.0	36.8	38.8	49
50	44.4	21.3	22.3	19.7	13.4	30.1	31.7	37.6	39.6	50
51	45.3	21.7	22.8	20.2	13.9	30.7	32.4	38.4	40.4	51
52	46.2	22.2	23.2	20.7	14.3	31.4	33.0	39.2	41.3	52
53	47.1	22.6	23.7	21.1	14.8	32.1	33.7	40.0	42.1	53
54	48.0	23.0	24.1	21.6	15.2	32.7	34.4	40.8	42.9	54
55	48.9	23.5	24.6	22.0	15.7	33.4	35.1	41.6	43.8	55
56	49.7	23.9	25.0	22.5	16.2	34.0	35.8	42.4	44.6	56
57	50.6	24.3	25.5	22.9	16.6	34.7	36.5	43.2	45.4	57
58	51.5	24.8	25.9	23.4	17.1	35.4	37.2	44.0	46.3	58
59	52.4	25.2	26.4	23.9	17.5	36.0	37.9	44.8	47.1	59
60	53.3	25.6	26.8	24.3	18.0	36.7	38.6	45.6	48.0	60
61	54.2	26.1	27.3	24.8	18.5	37.3	39.3	46.3	48.8	61
62	55.1	26.5	27.7	25.2	18.9	38.0	40.0	47.1	49.6	62
63	56.0	27.0	28.2	25.7	19.4	38.6	40.7	47.9	50.5	63
64	56.8	27.4	28.6	26.2	19.8	39.3	41.4	48.7	51.3	64

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
65	57.7	27.8	29.1	26.6	20.3	40.0	42.1	49.5	52.1	65
66	58.6	28.3	29.5	27.1	20.8	40.6	42.8	50.3	53.0	66
67	59.5	28.7	30.1	27.5	21.2	41.3	43.5	51.1	53.8	67
68	60.4	29.2	30.4	28.0	21.7	41.9	44.2	51.9	54.6	68
69	61.3	29.6	30.9	28.5	22.2	42.6	44.8	52.7	55.5	69
70	62.2	30.0	31.3	28.9	22.6	43.3	45.5	53.5	56.3	70
71	63.1	30.5	31.8	29.4	23.1	43.9	46.2	54.3	57.1	71
72	64.0	30.9	32.3	29.8	23.5	44.6	46.9	55.1	58.0	72
73	64.8	31.4	32.7	30.3	24.0	45.2	47.6	55.9	58.8	73
74	65.7	31.8	33.2	30.8	24.5	45.9	48.3	56.7	59.6	74
75	66.6	32.2	33.6	31.2	24.9	46.6	49.0	57.5	60.5	75
76	67.5	32.7	34.1	31.7	25.4	47.2	49.7	58.2	61.3	76
77	68.4	33.1	34.5	32.1	25.9	47.9	50.4	59.0	62.1	77
78	69.3	33.6	35.0	32.6	26.3	48.5	51.1	59.8	63.0	78
79	70.2	34.0	35.4	33.1	26.8	49.2	51.8	60.6	63.8	79
80	71.1	34.4	35.9	33.5	27.3	49.9	52.5	61.4	64.6	80
81	71.9	34.9	36.3	34.0	27.7	50.5	53.2	62.2	65.5	81
82	72.8	35.3	36.8	34.5	28.2	51.2	53.9	63.0	66.3	82
83	73.7	35.8	37.3	34.9	28.6	51.8	54.6	63.8	67 1	83
84	74.6	36.2	37.7	35.4	29.1	52.5	55.3	64.6	68.0	84
85	75.5	36.7	38.2	35.8	29.6	53.1	56.0	65.4	68.8	85
86	76.4	37.1	38.6	36.3	30.0	53.8	56.6	66.2	69.7	86
87	77.3	37.5	39.1	36.8	30.5	54.5	57.3	67.0	70.5	87
88	78.2	38.0	39.5	37.2	31.0	55.1	58.0	67.8	71.3	88
89	79.1	38.4	40.0	37.7	31.4	55.8	58.7	68.5	72.2	89
90	79.9	38.9	40.4	38.2	31.9	56.4	59.4	69.3	73.0	90
91	80.8	39.3	40.9	38.6	32.4	57.1	60.1	70.1	73.8	91
92	81.7	39.8	41.4	39.1	32.8	57.8	60.8	70.9	74.7	92
93	82.6	40.2	41.8	39.6	33.3	58.4	61.5	71.7	75.5	93
94	83.5	40.6	42.3	40.0	33.8	59.1	62.2	72.5	76.3	94
95	84.4	41.1	42.7	40.5	34.2	59.7	62.9	73.3	77 2	95
96	85.3	41.5	43.2	41.0	34.7	60.4	63.6	74.1	78.0	96
97	86.2	42.0	43.7	41.4	35.2	61.1	64.3	74.9	78.8	97
98	87.1	42.4	44.1	41.9	35.6	61.7	65.0	75.7	79.7	98
99	87.9	42.9	44.6	42.4	36.1	62.4	65.7	76.5	80.5	99
100	88.8	43.3	45.0	42.8	36.6	63.0	66.4	77.3	81.3	100
101	89.7	43.8	45.5	43.3	37.0	63.7	67 1	78.1	82.2	101
102	90.6	44.2	46.0	43.8	37.5	64.4	67.8	78.8	83.0	102
103	91.5	44.7	46.4	44.2	38.0	65.0	68.5	79.6	83.8	103
104	92.4	45.1	46.9	44.7	38.5	65.7	69.1	80.4	84.7	104
105	93.3	45.5	47.3	45.2	38.9	66.4	69.8	81.2	85.5	105
106	94.2	46.0	47.8	45.6	39.4	67.0	70.5	82.0	86.3	106
107	95.0	46.4	48.3	46.1	39.9	67.7	71.2	82.8	87.2	107
108	95.9	46.9	48.7	46.6	40.3	68.3	71.9	83.6	88.0	108
109	96.8	47.3	49.2	47.0	40.8	69.0	72.6	84.4	88.8	109
110	97.7	47.8	49.6	47.5	41.3	69.7	73.3	85.2	89.7	110
111	98.6	48.2	50.1	48.0	41.7	70.3	74 0	86 0	90.5	111
112	99.5	48.7	50.6	48.4	42.2	71.0	74 7	86.8	91.3	112
113	100.4	49.1	51.0	48.9	42.7	71.6	75.4	87.6	92.2	113
114	101.3	49.6	51.5	49.4	43.2	72.3	76.1	88.4	93.0	114
115	102.2	50.0	51.9	49.8	43.6	73.0	76.8	89.2	93.9	115
116	103.0	50.5	52.4	50.3	44.1	73.6	77.5	90.0	94.7	116
117	103.9	50.9	52.9	50.8	44.6	74.3	78.2	90.7	95.5	117
118	104.8	51.4	53.3	51.2	45.0	75.0	78.9	91.5	96.4	118
119	105.7	51.8	53.8	51.7	45.5	75.6	79.6	92.3	97.2	119

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
120	106.6	52.3	54.3	52.2	46.0	76.3	80.3	93.1	98.0	120
121	107.5	52.7	54.7	52.7	46.5	76.9	81.0	93.9	98.9	121
122	108.4	53.2	55.2	53.1	46.9	77.6	81.7	94.7	99.7	122
123	109.3	53.6	55.7	53.6	47.4	78.3	82.4	95.5	100.5	123
124	110.1	54.1	56.1	54.1	47.9	78.9	83.1	96.3	101.4	124
125	111.0	54.5	56.6	54.5	48.3	79.6	83.8	97.1	102.2	125
126	111.9	55.0	57.0	55.0	48.8	80.3	84.5	97.9	103.0	126
127	112.8	55.4	57.5	55.5	49.3	80.9	85.2	98.7	103.9	127
128	113.7	55 9	58.0	55.9	49.8	81.6	85.9	99.4	104.7	128
129	114.6	56.3	58.4	56.4	50.2	82.2	86.6	100.2	105.5	129
130	115.5	56.8	58.9	56.9	50.7	82.9	87.3	101.0	106.4	130
131	116.4	57.2	59.4	57.4	51.2	83.6	88.0	101.8	107.2	131
132	117.3	57.7	59.8	57.8	51.7	84.2	88.7	102.6	108.0	132
133	118.1	58.1	60.3	58.3	52.1	84.9	89.4	103.4	108.9	133
134	119.0	58.6	60.8	58.8	52.6	85.5	90.1	104.2	109.7	134
135	119.9	59.0	61.2	59.3	53.1	86.2	90.8	105.0	110.5	135
136	120.8	59.5	61.7	59.7	53.6	86.9	91.5	105.8	111.4	136
137	121.7	60.0	62.2	60.2	54.0	87.5	92.1	106.6	112.2	137
138	122.6	60.4	62.6	60.7	54.5	88.2	92.8	107.4	113.0	138
139	123.5	60.9	63.1	61.2	55.0	88.9	93.5	108.2	113.9	139
140	124.4	61.3	63.6	61.6	55.5	89.5	94.2	109.0	114.7	140
141	125.2	61.8	64.0	62.1	55.9	90.2	94.9	109.8	115.5	141
142	126.1	62.2	64.5	62.6	56.4	90.8	95.6	110.5	116.4	142
143	127.0	62.7	65.0	63.1	56.9	91.5	96.3	111.3	117.2	143
144	127.9	63.1	65.4	63.5	57.4	92.2	97.0	112.1	118.0	144
145	128 8	63.6	65.9	64.0	57.8	92.8	97.7	112.9	118.9	145
146	129.7	64.0	66.4	64.5	58.3	93.5	98.4	113.7	119.7	146
147	130.6	64.5	66.9	65.0	58.8	94.2	99.1	114.5	120.5	147
148	131 5	65.0	67.3	65.4	59.3	94.8	99.8	115.3	121.4	148
149	132.4	65.4	67.8	65.9	59.7	95.5	100.5	116.1	122.2	149
150	133.2	65.9	68.3	66.4	60.2	96.1	101.2	116.9	123.0	150
151	134.1	66.3	68.7	66.9	60.7	96.8	101.9	117.7	123.9	151
152	135.0	66.8	69.2	67.3	61.2	97.5	102.6	118.5	124.7	152
153	135.9	67.2	69.7	67.8	61.7	98.1	103.3	119.3	125.5	153
154	136.8	67.7	70.1	68.3	62.1	98.8	104.0	120.0	126.4	154
155	137.7	68.2	70.6	68.8	62.6	99.5	104.7	120.8	127.2	155
156	138.6	68.6	71.1	69.2	63.1	100.1	105.4	121.6	128.0	156
157	139.5	69.1	71.6	69.7	63.6	100.8	106.1	122.4	128.9	157
158	140.3	69.5	72.0	70.2	64.1	101.5	106.8	123.2	129.7	158
159	141.2	70.0	72.5	70.7	64.5	102.1	107.5	124.0	130.5	159
160	142.1	70.4	73.0	71.2	65.0	102.8	108.2	124.8	131.4	160
161	143.0	70.9	73.4	71.6	65.5	103.4	108.9	125.6	132.2	161
162	143.9	71.4	73.9	72.1	66.0	104.1	109.6	126.4	133.0	162
163	144.8	71.8	74.4	72.6	66.5	104.8	110.3	127.2	133.9	163
164	145.7	72.3	74.9	73.1	66.9	105.4	111.0	128.0	134.7	164
165	146.6	72.8	75.3	73.6	67.4	106.1	111.7	128.8	135.5	165
166	147.5	73.2	75.8	74.0	67.9	–06.8	112.4	129.6	136.4	166
167	148.3	73.7	76.3	74.5	68.4	107.4	113.1	130.3	137.2	167
168	149.2	74.1	76.8	75.0	68.9	108.1	113.8	131.1	138.0	168
169	150.1	74.6	77.2	75.5	69.3	108.8	114.5	131.9	138.9	169
170	151.0	75.1	77.7	76.0	69.8	109.4	115.2	132.7	139.7	170
171	151.9	75.5	78.2	76.4	70.3	110.1	115.9	133.5	140.5	161
172	152.8	76.0	78.7	76.9	70.8	111.8	116.6	134.3	141.4	172
173	153.7	76.4	79.1	77.4	71.3	111.4	117.3	135.1	142.2	173
174	154.6	76.9	79.6	77.9	71.7	112.1	118.0	135.9	143.0	174

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
175	155.5	77.4	80.1	78.4	72.2	112.8	118.7	136.7	143.9	175
176	156.3	77.8	80.6	78.8	72.7	113.4	119.4	137.5	144.7	176
177	157.2	78.3	81.0	79.3	73.2	114.1	120.1	138.3	145.5	177
178	158.1	78.8	81.5	79.8	73.7	114.8	120.8	139.1	146.4	178
179	159.0	79.2	82.0	80.3	74.2	115.4	121.5	139.8	147.2	179
180	159.9	79.7	82.5	80.8	74.6	116.1	122.2	140.6	148.0	180
181	160.8	80.1	82.9	81.3	75.1	116.7	122.9	141.4	148.9	181
182	161.7	80.6	83.4	81.7	75.6	117.4	123.6	142.2	149.7	182
183	162.6	81.1	83.9	82.2	76.1	118.1	124.3	143.0	150.5	183
184	163.4	81.5	84.4	82.7	76.6	118.7	125.0	143.8	151.4	184
185	164.3	82.0	84.9	83.2	77.1	119.4	125.7	144.6	152.2	185
186	165.2	82.5	85.3	83.7	77.6	120.1	126.4	145.4	153.0	186
187	166.1	82.9	85.8	84.2	78.0	120.7	127.1	146.2	153.9	187
188	167.0	83.4	86.3	84.6	78.5	121.4	127.8	147.0	154.7	188
189	167.9	83.9	86.8	85.1	79.0	122.1	128.5	147.8	155.5	189
190	168.8	84.3	87.2	85.6	79.5	122.7	129.2	148.6	156.4	190
191	169.7	84.8	87.7	86.1	80.0	123.4	129.9	149.3	157.2	191
192	170.5	85.3	88.2	86.6	80.5	124.1	130.6	150.1	158.0	192
193	171.4	85.7	88.7	87.1	81.0	125.7	131.3	150.9	158.9	193
194	172.3	86.2	89.2	87.6	81.4	125.4	132.0	151.7	159.7	194
195	173.2	86.7	89.6	88.0	81.9	126.1	132.7	152.5	160.5	195
196	174.1	87.1	90.1	88.5	82.4	126.7	133.4	153.3	161.4	196
197	175.0	87.6	90.6	89.0	82.9	127.4	134.1	154.1	162.2	197
198	175.9	88.1	91.1	89.5	83.4	128.1	134.8	154.9	163.0	198
199	176.8	88.5	91.6	90.0	83.9	128.7	135.5	155.7	163.9	199
200	177.7	89.0	92.0	90.5	84.4	129.4	136.2	156.5	164.7	200
201	178.5	89.5	92.5	91.0	84.8	130.0	136.9	157.3	165.5	201
202	179.4	89.9	93.0	91.4	85.3	130.7	137.6	158.1	166.4	202
203	180.3	90.4	93.5	91.9	85.8	131.4	138.3	158.8	167.2	203
204	181.2	90.9	94.0	92.4	86.3	132.0	139.0	159.6	168.0	204
205	182.1	91.4	94.5	92.9	86.8	132.7	139.7	160.4	168.9	205
206	183.0	91.8	94.9	93.4	87.3	133.4	140.4	161.2	169.7	206
207	183.9	92.3	95.4	93.9	87.8	134.0	141.1	162.0	170.5	207
208	184.8	92.8	95.9	94.4	88.3	134.7	141.8	162.8	171.4	208
209	185.6	93.2	96.4	94.9	88.8	135.4	142.5	163.6	172.2	209
210	186.5	93.7	96.9	95.4	89.2	136.0	143.2	164.4	173.0	210
211	187.4	94.2	97.4	95.8	89.7	136.7	143.9	165.2	173.8	211
212	188.3	94.6	97.8	96.3	90.2	137.4	144.6	166.0	174.7	212
213	189.2	95.1	98.3	96.8	90.7	138.0	145.3	166.8	175.5	213
214	190.1	95.6	98.8	97.3	91.2	138.7	146.0	167.5	176.4	214
215	191.0	96.1	99.3	97.8	91.7	139.4	146.7	168.3	177.2	215
216	191.9	96.5	99.8	98.3	92.2	140.0	147.4	169.1	178.0	216
217	192.8	97.0	100.3	98.8	92.7	140.7	148.1	169.9	178.9	217
218	193.6	97.5	100.8	99.3	93.2	141.4	148.8	170.7	179.7	218
219	194.5	98.0	101.2	99.8	93.7	142.0	149.5	171.5	180.5	219
220	195.4	98.4	101.7	100.3	94.2	142.7	150.2	172.3	181.4	220
221	196.3	98.9	102.2	100.8	94.7	143.4	150.9	173.1	182.2	221
222	197.2	99.4	102.7	101.2	95.1	144.0	151.6	173.9	183.0	222
223	198.1	99.9	103.2	101.7	95.6	144.7	152.3	174.7	183.9	223
224	199.0	100.3	103.7	102.2	96.1	145.4	153.0	175.5	184.7	224
225	199.9	100.8	104.2	102.7	96.6	146.0	153.7	176.2	185.5	225
226	200.7	101.3	104.6	103.2	97.1	146.7	154.4	177.0	186.4	226
227	201.6	101.8	105.1	103.7	97.6	147.4	155.1	177.8	187.2	227
228	202.5	102.2	106.6	104.2	98.1	148.0	155.8	178.6	188.0	228
229	203.4	102.7	106.1	104.7	98.6	148.7	156.5	179.4	188 8	229

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
230	204.3	103.2	106.6	105.2	99.1	149.4	157.2	180.2	189.7	230
231	205.2	103.7	107.1	105.7	99.6	150.0	157.9	181.0	190.5	231
232	206.1	104.1	107.6	106.2	100.1	150.7	158.6	181.8	191.3	232
233	207.0	104.6	108.1	106.7	100.6	151.4	159.3	182.6	192.2	233
234	207.9	105.1	108.6	107.2	101.1	152.0	160.0	183.4	193.0	234
235	208.7	105.6	109.1	107.7	101.6	152.7	160.7	184.2	193.8	235
236	209.6	106.0	109.5	108.2	102.1	153.4	161.4	184.9	194.7	236
237	210.5	106.5	110.0	108.7	102.6	154.0	162.1	185.7	195.5	237
238	211.4	107.0	110.5	109.2	103.1	154.7	162.8	186.5	196.3	238
239	212.3	107.5	111.0	109.6	103.5	155.4	163.5	187.3	197.2	239
240	213.2	108.0	111.5	110.1	104.0	156.1	164.3	188.1	198.0	240
241	214.1	108.4	112.0	110.6	104.5	156.7	165.0	188.9	198.8	241
242	215.0	108.9	112.5	111.1	105.0	157.4	165.7	189.7	199.7	242
243	215.8	109.4	113.0	111.6	105.5	158.1	166.4	190.5	200.5	243
244	216.7	109.9	113.5	112.1	106.0	158.7	167.1	191.3	201.3	244
245	217.6	110.4	114.0	112.6	106.5	159.4	167.8	192.1	202.2	245
246	218.5	110.8	114.5	113.1	107.0	160.1	168.5	192.9	203.0	246
247	219.4	111.3	115.0	113.6	107.5	160.7	169.2	193.6	203.8	247
248	220.3	111.8	115.4	114.1	108.0	161.4	169.9	194.4	204.7	248
249	221.2	112.3	115.9	114.6	108.5	162.1	170.6	195.2	205.5	249
250	222.1	112.8	116.4	115.1	109.0	162.7	171.3	196.0	206.3	250
251	223.0	113.2	116.9	115.6	109.5	163.4	172.0	196.8	207.2	251
252	223.8	113.7	117.4	116.1	110.0	164.1	172.7	197.6	208.0	252
253	224.7	114.2	117.9	116.6	110.5	164.7	173.4	195.4	208.8	253
254	225.6	114.7	118.4	117.1	111.0	165.4	174.1	199.2	209.7	254
255	226.5	115.2	118.9	117.6	111.5	166.1	174.8	200.0	210.5	255
256	227.4	115.7	119.4	118.1	112.0	166.8	175.5	200.8	211.3	256
257	228.3	116.1	119.9	118.6	112.5	167.4	176.2	201.6	212.2	257
258	229.2	116.6	120.4	119.1	113.0	168.1	176.9	202.3	213.0	258
259	230.1	117.1	120.9	119.6	113.5	168.8	177.6	203.1	213.8	259
260	231.0	117.6	121.4	120.1	114.0	169.4	178.3	203.9	214.7	260
261	231.8	118.1	121.9	120.6	114.5	170.1	179.0	204.7	215.5	261
262	232.7	118.6	122.4	121.1	115.0	170.8	179.8	205.5	216.3	262
263	233.6	119.0	122.9	121.6	115.5	171.4	180.5	206.3	217.2	263
264	234.5	119.5	123.4	122.1	116.0	172.1	181.2	207.1	218.0	264
265	235.4	120.0	123.9	122.6	116.5	172.8	181.9	207.9	218.8	265
266	236.3	120.5	124.4	123.1	117.0	173.5	182.6	208.7	219.7	266
267	237.2	121.0	124.9	123.6	117.5	174.1	183.3	209.5	220.5	267
268	238.1	121.5	125.4	124.1	118.0	174.8	184.0	210.3	221.3	268
269	238.9	122.0	125.9	124.6	118.5	175.5	184.7	211.0	222.1	269
270	239.8	122.5	126.4	125.1	119.0	175.1	185.4	211.8	223.0	270
271	240.7	122.9	126.9	125.6	119.5	176.8	186.1	212.6	223.8	271
272	241.6	123.4	127.4	126.2	120.0	177.5	186.8	213.4	224.6	272
273	242.5	123.9	127.9	126.7	120.6	178.1	187.5	214.2	225.5	273
274	243.4	124.4	128.4	127.2	121.1	178.8	188.2	215.0	226.3	274
275	244.3	124.9	128.9	127.7	121.6	179.5	188.9	215.8	227.1	275
276	245.2	125.4	129.4	128.2	122.1	180.2	189.6	216.6	228.0	276
277	246.1	125.9	129.9	128.7	122.6	180.8	190.3	217.4	228.8	277
278	246.9	126.4	130.4	129.2	123.1	181.5	191.0	218.2	229.6	278
279	247.8	126.9	130.9	129.7	123.6	182.2	191.7	218.9	230.5	279
280	248.7	127.3	131.4	130.2	124.1	182.8	192.4	219.7	231.3	280
281	249.6	127.8	131.9	130.7	124.6	183.5	193.1	220.5	232.1	281
282	250.5	128.3	132.4	131.2	125.1	184.2	193.9	221.3	233.0	282
283	251.4	128.8	132.9	131.7	125.6	184.8	194.6	222.1	233.8	283
284	252.3	129.3	133.4	132.2	126.1	185.5	195.3	222.9	234.6	284

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
285	253.2	129.8	133.9	132.7	126.6	186.2	196.0	223.7	235.5	285
286	254.0	130.3	134.4	133.2	127.1	186.9	196.7	224.5	236.3	286
287	254.9	130.8	134.9	133.7	127.6	187.5	197.4	225.3	237.1	287
288	255.8	131.3	135.4	134.3	128.1	188.2	198.1	226.1	238.0	288
289	256.7	131.8	135.9	134.8	128.6	188.9	198.8	226.9	238.8	289
290	257.6	132.3	136.4	135.3	129.2	189.5	199.5	227.6	239.6	290
291	258.5	132.7	136.9	135.8	129.7	190.2	200.2	228.4	240.5	291
292	259.4	133.2	137.4	136.3	130.2	190.9	200.9	229.2	241.3	292
293	260.3	133.7	137.9	136.8	130.7	191.5	201.6	230.0	242.1	293
294	261.2	134.2	138.4	137.3	131.2	192.2	202.3	230.8	242.9	294
295	262.0	134.7	138.9	137.8	131.7	192.9	203.0	231.6	243.8	295
296	262.9	135.2	139.4	138.3	132.2	193.6	203.7	232.4	244.6	296
297	263.8	135.7	140.0	138.8	132.7	194.2	204.4	233.2	245.4	297
298	264.7	136.2	140.5	139.4	133.2	194.9	205.1	234.0	246.3	298
299	265.6	136.7	141.0	139.9	133.7	195.6	205.8	234.8	247.1	299
300	266.5	137.2	141.5	140.4	134.2	196.2	206.6	235.5	247.9	300
301	267.4	137.7	142.0	140.9	134.8	196.9	207.3	236.3	248.8	301
302	268.3	138.2	142.5	141.4	135.3	197.6	208.0	237.1	249.6	302
303	269.1	138.7	143.0	141.9	135.8	198.3	208.7	237.9	250.4	303
304	270.0	139.2	143.5	142.4	136.3	198.9	209.4	238.7	251.3	304
305	270.9	139.7	144.0	142.9	136.8	199.6	210.1	239.5	252.1	305
306	271.8	140.2	144.5	143.4	137.3	200.3	210.8	240.3	252.9	306
307	272.7	140.7	145.0	144.0	137.8	201.0	211.5	241.1	253.8	307
308	273.6	141.2	145.5	144.5	138.3	201.6	212.2	241.9	254.6	308
309	274.5	141.7	146.1	145.0	138.8	202.3	212.9	242.7	255.4	309
310	275.4	142.2	146.6	145.5	139.4	203.0	213.7	243.5	256.3	310
311	276.3	142.7	147.1	146.0	139.9	203.6	214.4	244.2	257.1	311
312	277.1	143.2	147.6	146.5	140.4	204.3	215.1	245.0	257.9	312
313	278.0	143.7	148.1	147.0	140.9	205.0	215.8	245.8	258.8	313
314	278.9	144.2	148.6	147.6	141.4	205.7	216.5	246.6	259.6	314
315	279.8	144.7	149.1	148.1	141.9	206.3	217.2	247.4	260.4	315
316	280.7	145.2	149.6	148.6	142.4	207.0	217.9	248.2	261.2	316
317	281.6	145.7	150.1	149.1	143.0	207.7	218.6	249.0	262.1	317
318	282.5	146.2	150.7	149.6	143.5	208.4	219.3	249.8	262.9	318
319	283.4	146.7	151.2	150.1	144.0	209.0	220.0	250.6	263.7	319
320	284.2	147.2	151.7	150.7	144.5	209.7	220.7	251.3	264.6	320
321	285.1	147.7	152.2	151.2	145.0	210.4	221.4	252.1	265.4	321
322	286.0	148.2	152.7	151.7	145.5	211.0	222.2	252.9	266.2	322
323	286.9	148.7	153.2	152.2	146.0	211.7	222.9	253.7	267.1	323
324	287.8	149.2	153.7	152.7	146.6	212.4	223.6	254.5	267.9	324
325	288.7	149.7	154.3	153.2	147.1	213.1	224.3	255.3	268.7	325
326	289.6	150.2	154.8	153.8	147.6	213.7	225.0	256.1	269.6	326
327	290.5	150.7	155.3	154.3	148.1	214.4	225.7	256.9	270.4	327
328	291.4	151.2	155.8	154.8	148.6	215.1	226.4	257.7	271.2	328
329	292.2	151.7	156.3	155.3	149.1	215.8	227.1	258.5	272.1	329
330	293.1	152.2	156.8	155.8	149.7	216.4	227.8	259.3	272.9	330
331	294.0	152.7	157.3	156.4	150.2	217.1	228.5	260.0	273.7	331
332	294.9	153.2	157.9	156.9	150.7	217.8	229.2	260.8	274.6	332
333	295.8	153.7	158.4	157.4	151.2	218.4	230.0	261.6	275.4	333
334	296.7	154.2	158.9	157.9	151.7	219.1	230.7	262.4	276.2	334
335	297.6	154.7	159.4	158.4	152.3	219.8	231.4	263.2	277.0	335
336	298.5	155.2	159.9	159.0	152.8	220.5	232.1	264.0	277.9	336
337	299.3	155.8	160.5	159.5	153.3	221.1	232.8	264.8	278.7	337
338	300.2	156.3	161.0	160.0	153.8	221.8	233.5	265.6	279.5	338
339	301.1	156.8	161.5	160.5	154.3	222.5	234.2	266.4	280.4	339

MUNSON AND WALKER'S TABLE—*Continued*

Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
340	302.0	157.3	162.0	161.0	154.8	223.2	234.9	267.1	281.2	340
341	302.9	157.8	162.5	161.6	155.4	223.8	235.6	267.9	282.0	341
342	303.8	158.3	163.1	162.1	155.9	224.5	236.3	268.7	282.9	342
343	304.7	158.8	163.6	162.6	156.4	225.2	237.0	269.5	283.7	343
344	305.6	159.3	164.1	163.1	156.9	225.9	237.8	270.3	284.5	344
345	306.5	159.8	164.6	163.7	157.5	226.5	238.5	271.1	285.4	345
346	307.3	160.3	165.1	164.2	158.0	227.2	239.2	271.9	286.2	346
347	308.2	160.8	165.7	164.7	158.5	227.9	239.9	272.7	287.0	347
348	309.1	161.4	166.2	165.2	159.0	228.5	240.6	273.5	287.9	348
349	310.0	161.9	166.7	165.7	159.5	229.2	241.3	274.3	288.7	349
350	310.9	162.4	167.2	166.3	160.1	229.9	242.0	275.0	289.5	350
351	311.8	162.9	167.7	166.8	160.6	230.6	242.7	275.8	290.4	351
352	312.7	163.4	168.3	167.3	161.1	231.2	243.4	276.6	291.2	352
353	313.6	163.9	168.8	167.8	161.6	231.9	244.1	277.4	292.0	353
354	314.4	164.4	169.3	168.4	162.2	232.6	244.8	278.2	292.8	354
355	315.3	164.9	169.8	168.9	162.7	233.3	245.6	279.0	293.7	355
356	316.2	165.4	170.4	169.4	163.2	233.9	246.3	279.8	294.5	356
357	317.1	166.0	170.9	170.0	163.7	234.6	247.0	280.6	295.3	357
358	318.0	166.5	171.4	170.5	164.3	235.3	247.7	281.4	296.2	358
359	318.9	167.0	171.9	171.0	164.8	236.0	248.4	282.2	297.0	359
360	319.8	167.5	172.5	171.5	165.3	236.7	249.1	282.9	297.8	360
361	320.7	168.0	173.0	172.1	165.8	237.3	249.8	283.7	298.7	361
362	321.6	168.5	173.5	172.6	166.4	238.0	250.5	284.5	299.5	362
363	322.4	169.0	174.0	173.1	166.9	238.7	251.2	285.3	300.3	363
364	323.3	169.6	174.6	173.7	167.4	239.4	252.0	286.1	301.2	364
365	324.2	170.1	175.1	174.2	167.9	240.0	252.7	286.9	302.0	365
366	325.1	170.6	175.6	174.7	168.5	240.7	253.4	287.7	302.8	366
367	326.0	171.1	176.1	175.2	169.0	241.4	254.1	288.5	303.6	367
368	326.9	171.6	176.7	175.8	169.5	242.1	254.8	289.3	304.5	368
369	327.8	172.1	177.2	176.3	170.0	242.7	255.5	290.0	305.3	369
370	328.7	172.7	177.7	176.8	170.6	243.4	256.2	290.8	306.1	370
371	329.5	173.2	178.3	177.4	171.1	244.1	256.9	291.6	307.0	371
372	330.4	173.7	178.8	177.9	171.6	244.8	257.7	292.4	307.8	372
373	331.3	174.2	179.3	178.4	172.2	245.4	258.4	292.2	308.6	373
374	332.2	174.7	179.8	179.0	172.7	246.1	259.1	294.0	309.5	374
375	333.1	175.3	180.4	179.5	173.2	246.8	259.8	294.8	310.3	375
376	334.0	175.8	180.9	180.0	173.7	247.5	260.5	295.6	311.1	376
377	334.9	176.3	181.4	180.6	174.3	248.1	261.2	296.4	312.0	377
378	335.8	176.8	182.0	181.1	174.8	248.8	261.9	297.2	312.8	378
379	336.7	177.3	182.5	181.6	175.3	249.5	262.6	297.9	313.6	379
380	337.5	177.9	183.0	182.1	175.9	250.2	263.4	298.7	314.5	380
381	338.4	178.4	183.6	182.7	176.4	250.8	264.1	299.5	315.3	381
382	339.3	178.9	184.1	183.2	176.9	251.5	264.8	300.3	316.1	382
383	340.2	179.4	184.6	183.8	177.5	252.2	265.5	301.1	316.9	383
384	341.1	180.0	185.2	184.3	178.0	252.9	266.2	301.9	317.8	384
385	342.0	180.5	185.7	184.8	178.5	253.6	266.9	302.7	318.6	385
386	342.9	181.0	186.2	185.4	179.1	254.2	267.6	303.5	319.4	386
387	343.8	181.5	186.8	185.9	179.6	254.9	268.3	304.2	320.3	387
388	344.6	182.0	187.3	186.4	180.1	255.6	269.0	305.0	321.1	388
389	345.5	182.6	187.8	187.0	180.6	256.3	269.8	305.8	321.9	389
390	346.4	183.1	188.4	187.5	181.2	256.9	270.5	306.6	322.8	390
391	347.3	183.6	188.9	188.0	181.7	257.6	271.2	307.4	323.6	391
392	348.2	184.1	189.4	188.6	182.3	258.3	271.9	308.2	324.4	392
393	349.1	184.7	190.0	189.1	182.8	259.0	272.6	309.0	325.2	393
394	350.0	185.2	190.5	189.7	183.3	259.6	273.3	309.8	326.1	394

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
395	350.9	185.7	191.0	190.2	183.9	260.3	274.0	310.6	326.9	395
396	351.8	186.2	191.6	190.7	184.4	261.0	274.7	311.4	327.7	396
397	352.6	186.8	192.1	191.3	184.9	261.7	275.5	312.1	328.6	397
398	353.5	187.3	192.7	191.8	185.5	262.3	276.2	312.9	329.4	398
399	354.4	187.8	193.2	192.3	186.0	263.0	276.9	313.7	330.2	399
400	355.3	188.4	193.7	192.9	186.5	263.7	277.6	314.5	331.1	400
401	356.2	188.9	194.3	193.4	187.1	264.4	278.3	315.3	331.9	401
402	357.1	189.4	194.8	194.0	187.6	265.0	279.0	316.1	332.7	402
403	358.0	189.9	195.4	194.5	188.1	265.7	279.7	316.9	333.6	403
404	358.9	190.5	195.9	195.0	188.7	266.4	280.4	317.7	334.4	404
405	359.7	191.0	196.4	195.6	189.2	267.1	281.1	318.5	335.2	405
406	360.6	191.5	197.0	196.1	189.8	267.8	281.9	319.2	336.0	406
407	361.5	192.1	197.5	196.7	190.3	268.4	282.6	320.0	336.9	407
408	362.4	192.6	198.1	197.2	190.8	269.1	283.3	320.8	337.7	408
409	363.3	193.1	198.6	197.7	191.4	269.8	284.0	321.6	338.5	409
410	364.2	193.7	199.1	198.3	191.9	270.5	284.7	322.4	339.4	410
411	365.1	194.2	199.7	198.8	192.5	271.2	285.4	323.2	340.2	411
412	366.0	194.7	200.2	199.4	193.0	271.8	286.2	324.0	341.0	412
413	366.9	195.2	200.8	199.9	193 5	272.5	286.9	324.8	341.9	413
414	367.7	195.8	201.3	200.5	194.1	273.2	287.6	325.6	342.7	414
415	368.6	196.3	201.8	201.0	194.6	273.9	288.3	326.3	343.5	415
416	369.5	196.8	202.4	201.6	195.2	274.6	289.0	327.1	344.4	416
417	370.4	197.4	202.9	202.1	195.7	275.2	289.7	327.9	345.2	417
418	371.3	197.9	203.5	202.6	196.2	275.9	290.4	328.7	346.0	418
419	372.2	198.4	204.0	203.2	196.8	276.6	291.2	329.5	346.8	419
420	373.1	199.0	204.6	203.7	197.3	277.3	291.9	330.3	347.7	720
421	374.0	199.5	205.1	204.3	197.9	277.9	292.6	331.1	348.5	421
422	374.8	200 1	205.7	204.8	198.4	278.6	293.3	331.9	349.3	422
423	375.7	200.6	206.2	205.4	198.9	279.3	294.0	332.7	350.2	423
424	376.6	201.1	206.7	205.9	199.5	280.0	294.7	333.4	351.0	424
425	377.5	201.7	207.3	206.5	200.0	280.7	295.4	334.2	351.8	425
426	378.4	202.2	207.8	207.0	200.6	281.3	296.2	335.0	352.7	426
427	379.3	202.8	208.4	207.6	201.1	282.0	296.9	335.8	353.5	427
428	380.2	203.3	208.9	208.1	201.7	282.7	297.6	336.6	354.3	428
429	381.1	203.8	209.5	208.7	202.2	283.4	298.3	337.4	355.1	429
430	382.0	204.4	210.0	209.2	202.7	284.1	299.0	338.2	356.0	430
431	382.8	204.9	210.6	209.8	203.3	284.7	299.7	339.0	356.8	431
432	383.7	205.5	211.1	210.3	203.8	285.4	300.5	339.7	357.6	432
433	384.6	206.0	211.7	210.9	204.4	286.1	301.2	340.5	358.5	433
434	385.5	206.5	212.2	211.4	204.9	286.8	301.9	341.3	359.3	434
435	386.4	207.1	212.8	212.0	205.5	287.5	302.6	342.1	360.1	435
436	387.3	207.6	213.3	212.5	206.0	288.1	303.3	342.9	361.0	436
437	388.2	208.2	213.9	213.1	206.6	288.8	304.0	343.7	361.8	437
438	389.1	208.7	214.4	213.6	207.1	289.5	304.7	344.5	362.6	438
439	390.0	209.2	215.0	214.2	207.7	290.2	305.5	345.3	363.4	439
440	390.8	209.8	215.5	214.7	208.2	290.9	306.2	346.1	364.3	440
441	391.7	210.3	216.1	215.3	208.8	291.5	306.9	346.8	365.1	441
442	392.6	210.9	216.6	215.8	209.3	292.2	307.6	347.6	365.9	442
443	393.5	211.4	217.2	216.4	209.9	292.9	308.3	348.4	366.8	443
444	394.4	212.0	217.8	216.9	210.4	293.6	309.0	349.2	367.6	444
445	395.3	212.5	218.3	217.5	211.0	294.2	309.7	350.0	368.4	445
446	396.2	213.1	218.9	218.0	211.5	294.9	310.5	350.8	369.3	446
447	397.1	213.6	219.4	218.6	212.1	295.6	311.2	351.6	370.1	447
448	397.9	214.1	220.0	219.1	212.6	296.3	311.9	352.4	370.9	448
449	398.8	214.7	220.5	219.7	213.2	297.0	312.6	353.2	371.7	449

MUNSON AND WALKER'S TABLE—*Continued*

[Expressed in milligrams.]

Cuprous Oxide (Cu_2O)	Copper (Cu)	Dextrose (*d*-Glucose)	Invert Sugar	Invert Sugar and Sucrose		Lactose		Maltose		Cuprous Oxide (Cu_2O)
				0.4 Gram Total Sugar	2 Grams Total Sugar	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	$C_{12}H_{22}O_{11}$	$C_{12}H_{22}O_{11}H_2O$	
450	399.7	215.2	221.1	220.2	213.7	297.6	313.3	353.9	372.6	450
451	400.6	215.8	221.6	220.8	214.3	298.3	314.0	354.7	373.4	451
452	401.5	216.3	222.2	221.4	214.8	299.0	314.7	355.5	374.2	452
453	402.4	216.9	222.8	221.9	215.4	299.7	315.5	356.3	375.1	453
454	403.3	217.4	223.3	222.5	215.9	300.4	316.2	357.1	375.9	454
455	404.2	218.0	223.9	223.0	216.5	301.1	316.9	357.9	376.7	455
456	405.1	218.5	224.4	223.6	217.0	301.7	317.6	358.7	377.6	456
457	405.9	219.1	225.0	224.1	217.6	302.4	318.3	359.5	378.4	457
458	406.8	219.6	225.5	224.7	218.1	303.1	319.0	360.3	379.2	458
459	407.7	220.2	226.1	225.3	218.7	303.8	319.8	361.0	380.0	459
460	408.6	220.7	226.7	225.8	219.2	304.5	320.5	361.8	380.9	460
461	409.5	221.3	227.2	226.4	219.8	305.1	321.2	362.6	381.7	461
462	410.4	221.8	227.8	226.9	220.3	305.8	321.9	363.4	382.5	462
463	411.3	222.4	228.3	227.5	220.9	306.5	322.6	364.2	383.4	463
464	412.2	222.9	228.9	228.1	221.4	307.2	323.4	365.0	384.2	464
465	413.0	223.5	229.5	228.6	222.0	307.9	324.1	365.8	385.0	465
466	413.9	224.0	230.0	229.2	222.5	308.6	324.8	366.6	385.9	466
467	414.8	224.6	230.6	229.7	223.1	309.2	325.5	367.3	386.7	467
468	415.7	225.1	231.2	230.3	223.7	309.9	326.2	368.1	387.5	468
469	416.6	225.7	231.7	230.9	224.2	310.6	326.9	368.9	388.3	469
470	417.5	226.2	232.3	231.4	224.8	311.3	327.7	369.7	389.2	470
471	418.4	226.8	232.8	232.0	225.3	312.0	328.4	370.5	390.0	471
472	419.3	227.4	233.4	232.5	225.9	312.6	329.1	371.3	390.8	472
473	420.2	227.9	234.0	233.1	226.4	313.3	329.8	372.1	391.7	473
474	421.0	228.5	234.5	233.7	227.0	314.0	330.5	372.9	392.5	474
475	421.9	229.0	235.1	234.2	227.6	314.7	331.3	373.7	393.3	475
476	422.8	229.6	235.7	234.8	228.1	315.4	332.0	374.4	394.2	476
477	423.7	230.1	236.2	235.4	228.7	316.1	332.7	375.2	395.0	477
478	424.6	230.7	236.8	235.9	229.2	316.7	333.4	376.0	395.8	478
479	425.5	231.3	237.4	236.5	229.8	317.4	334.1	376.8	396.6	479
480	426.4	231.8	237.9	237.1	230.3	318.1	334.8	377.6	397.5	480
481	427.3	232.4	238.5	237.6	230.9	318.8	335.6	378.4	398.3	481
482	428.1	232.9	239.1	238.2	231.5	319.5	336.3	379.2	399.1	482
483	429.0	233.5	239.6	238.8	232.0	320.1	337.0	380.0	400.0	483
484	429.9	234.1	240.2	239.3	232.6	320.8	337.7	380.7	400.8	484
485	430.8	234.6	240.8	239.9	233.2	321.5	338.4	381.5	401.6	485
486	431.7	235.2	241.4	240.5	233.7	322.2	339.1	382.3	402.4	486
487	432.6	235.7	241.9	241.0	234.3	322.9	339.9	383.1	403.3	487
488	433.5	236.3	242.5	241.6	234.8	323.6	340.6	383.9	404.1	488
489	434.4	236.9	243.1	242.2	235.4	324.2	341.3	384.7	404.9	489
490	435.3	237.4	243.6	242.7	236.0	324.9	342.0	385.5	405.8	490

COMMERCIAL GLUCOSE

Method I.—Tentative.—A.O.A.C.

(*Substances containing little or no invert sugar.*)

Commercial glucose cannot be determined accurately owing to the varying amounts of dextrin, maltose, and dextrose present in this product. However, in syrups, in which the amount of invert sugar is so

small as not to appreciably affect the result, commercial glucose may be estimated approximately by the following formula:

$$G=\frac{(a-S)100}{175},$$

in which

G = per cent of commercial glucose;
a = direct polarization;
S = per cent of cane sugar.

Express the results in terms of commercial glucose polarizing +175° V.

METHOD II.—TENTATIVE.—A.O.A.C.

(*Substances containing invert sugar.*)

Prepare an inverted half-normal solution of the substance as directed under "Sucrose," except that after inversion cool the solution, make neutral to phenolphthalein with sodium hydroxid solution, slightly acidify with hydrochloric acid, and treat with 5–10 mils of alumina cream before making up to the mark. Filter and polarize at 87° C. in a 200-mm. jacketed tube. Multiply the reading by 200 and divide by the factor 163 to express the amount of glucose present in terms of glucose polarizing +175° V.

ARSENIC

It is a good rule for the analyst in the field of medicinal chemistry to test every mixture for arsenic. In the more common forms, as arsenous acid, arsenic iodide, bromide, chloride, peptonate, or sulphide, the amount given at a dose is seldom more than $\frac{1}{20}-\frac{1}{5}$ of a grain, and from that amount it dwindles down to $\frac{1}{1000}$. During recent years it has been the custom to administer this element in some organic combination where, comparatively, the dose of the metal is much larger, thus in salvarsan many times the lethal dose can be tolerated than if in simple ionic condition. Again, its presence will be manifested in unexpected cases as an impurity, for instance in the coating of tablets where oxide of iron has been substituted for chocolate.

The Pharmacopœia prescribes a method for the assay of Fowler's solution, and there are procedures given for the examination of salvarsan and other pure organic substances which will be detailed later, but at this point we are concerned with the testing of mixtures containing arsenic. The simplest procedure for its determination is by a comparative Marsh mirror or mercuric chloride test paper. In this determination the steps include a careful oxidation of the organic matter, the manipulation of a Marsh test with the clear solution obtained by oxidation, and the com-

parison of the mirror or stain with a set of standards. The oxidation may be carried out with nitric and sulphuric acid, though Bishop claims that there is loss of arsenic by volatilization and advocates a modified oxidation which is subsequently described.

If the substance is a solid, 5 to 10 grams are weighed out and treated directly in a No. VI porcelain dish with 25–50 mils arsenic-free nitric acid and allowed to digest in the cold until the organic matter and most of the soluble mineral matter have gone into solution. If a liquid preparation is under examination, 25–50 mils should be evaporated over the steam bath and the residue treated with nitric acid. By this procedure a clear yellow to reddish liquid usually results, and the subsequent manipulation is greatly facilitated. The nitrated mixture is now treated with 15 mils of concentrated sulphuric acid and stirred cautiously without warming; if sugar is present in any great amount, there will be an energetic action and if there is danger of loss by contents frothing over, strong nitric acid should be quickly added in considerable quantity and the action will subside immediately. If the heat generated by the action is sufficient to drive off all the remaining nitric acid the residue will now be black, and a further quantity should be added, well mixed, and the dish carefully warmed over a low flame or on an electric hot plate running at a moderate temperature and covered with a watch glass. The charred residue will quickly decolorize, and if no subsequent charring takes place when the nitric acid is driven off, the procedure may be terminated, but if charring occurs again, the dish must be cooled, more nitric acid added and the heat again applied and this manipulation continued until a clear residue remains.

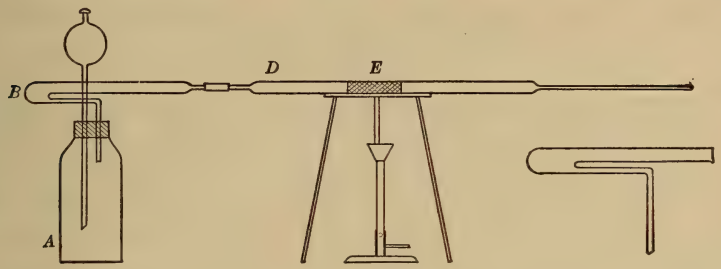
When the residue becomes cold it is transferred to a graduated flask of 100 mils capacity and made up to the mark with water. Aliquots of this solution are then introduced into the Marsh apparatus until a mirror is obtained which is suitable for comparison.

Individual workers usually prefer their own style of Marsh apparatus, and the author will not attempt to describe the multitudinous arrangements which are to be found in the different laboratories. If the worker uses the mirror test it is important that the glass be sufficiently hard to withstand a high heat, if not the tube will probably fuse and seal up and the stopper blow out of the generator or the tube may be kept too cool and some of the arsenic escape. The glass recommended is that having a bluish fluorescence when examined longitudinally.

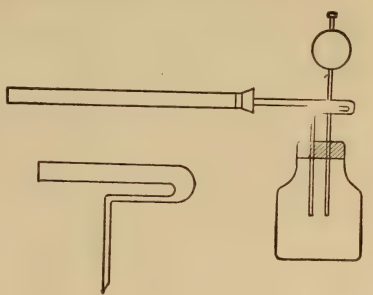
Two simple forms of apparatus and attachments are shown in the accompanying illustrations.

A is the generator fitted with a two-hole rubber stopper containing a small bulb separatory funnel and a bent tube *B* shown in greater detail on the side. The latter contains a loose wad of dry lead acetate paper,

then a small pledget of cotton, then granular calcium chloride and another small pledget of cotton. To this tube is attached the mirror tube of hard glass *D*, of about $\frac{1}{4}$ to $\frac{5}{8}$ in. inside diameter, which rests on a tripod, and is surrounded about 1 in. from the capillary end with a roll of copper gauze *E*, 2 in. wide. The tube is heated by a Bunsen burner fitted with a wing top. To start the apparatus use powdered 20-mesh zinc C. P.



free from arsenic and sulphuric acid 1–3. When beginning work with a newly constructed apparatus, the evolution of hydrogen will be extremely slow, often practically stagnant, but the introduction of a few drops of copper sulphate solution will start an energetic and steady evolution. After the apparatus has run for about eight minutes, the Bunsen should be lighted and observations made as to the purity of the reagents. If there is no deposit, the aliquot of the unknown mixture may be introduced through the separatory funnel and washed down into the generator with sulphuric acid 1–3.



It is not necessary to light the gas escaping at the outlet of the capillary tube.

When using the bichloride test-paper prepared by dipping strips of filter paper into a 5 per cent alcoholic solution of $HgCl_2$, the same form of generator and clarifying tube can be used and the combustion tube substituted by an ordinary glass tube into which the strip of test-paper is inserted. Every laboratory should have a set of standard mirrors or bichloride test-papers, prepared from a carefully standardized solution of arsenous acid, and they should be kept in the dark and replaced from time to time by new ones.

Bishop's[1] method is applicable to those substances which are soluble in or decomposed by hot concentrated sulphuric acid. A mixture of

[1] Jour. Amer. Chem. Soc., 28, 1906, 178–185.

hydrochloric and sulphurous acids is forced through a capillary tube into the hot sulphuric acid. After distilling for one hour while absorbing the escaping gas in water, the distillate containing arsenous chloride, hydrochloric and sulphurous acid, is oxidized with potassium chlorate, evapoated on the steam bath and the Marsh test applied.

Andrews and Farr[1] offer a volumetric method for estimating small quantities of arsenic which could probably be used after separating the arsenic from the other ingredients by oxidation or distillation. About 20 mils of the solution are mixed with 50 mils of a solution of 20 grams of stannous chloride and 40 grams tartaric acid in 1 liter 40 per cent hydrochloric acid, and the mixture heated for two to three hours at 35–40° C. in a well-stoppered bottle, until the precipitated arsenic has completely settled. The precipitate is washed onto an asbestos filter with the aid of strong hydrochloric acid free from chlorine and then the filter and precipitate are returned to the bottle with an amount of N/100 or N/10 iodine solution 10–100 per cent above that indicated by the equation:

$$As+5I+7\ NaHCO_3=Na_2HAsO_4+5NaI+7\ CO_2+3\ H_2O$$

Enough of a 5 per cent solution of sodium bicarbonate or phosphate is added to maintain neutrality, and when all the arsenic is dissolved, the excess of iodine is titrated with N/100 or N/1000 arsenite solution. For quantities of arsenic smaller than 0.5 milligram, N/1000 solution may be used, but in this case a correction must be made for the amount of iodine required to produce the end reaction.

[1] Amer. Jour. Sci., 1909, 27, 316–20.

CHAPTER II

CRUDE DRUG ASSAYS

Drug assaying requires a special technique which is acquired only after considerable experience. An accurate analyst understands the theory of the process and knows the reason for each step in the manipulation. Assay methods by the legion have been proposed and many of them have been studied by referees working with corps of collaborators. The results have sometimes shown wide variation and the reason is due sometimes to faults in the methods, but more often to the personal equation of the operators. It is the author's conclusion, after studying the results obtained by different workers on a given sample, that a wide variation in figures usually could be traced directly to inattention to details which are absolutely necessary in carrying out these delicate determinations. Analysts will offer themselves as competent to handle alkaloid assaying who have had practically no experience with drugs and perhaps none in handling the special apparatus required. They run through a single assay of a drug without preliminary practice and report their results to the consternation of the referee. There is no field of chemical work where one needs longer and more exact training than in manipulating alkaloids. It is admitted that in describing methods, little details essential for correct results are often omitted, and it might be assumed that a worker with chemical "sense" should be aware of them in their proper place, but this is not the case, and in nine cases out of ten they will be neglected. For instance, after shaking out the original percolate with acid, this acid solution should be shaken thoroughly with ether and allowed to separate completely, at least fifteen minutes, then run into another separator, the ether washed with a little water and this added to the acid, the solution being then ready for the alkali. Again, in all titration methods there is a considerable opportunity for error by dissolving in N/10 acid, using only 3–5 c.c. It would be better to dissolve in 20 c.c. of N/50 acid, which will reduce the error to a minimum, or if it is feared that a weak acid will not completely take up the alkaloid, dissolve the residue in neutral alcohol, adding acid and then titrating back; or if neutral alcohol is not feasible, dissolve in ordinary alcohol and run a blank. When a drug is shaken with a volatile solvent in a flask and then poured into a percolator, the

lip of the flask should be carefully washed with an additional quantity of solvent in order to remove any adhering alkaloid, which is always left there by the evaporation of the menstruum. The stem of the separator should be washed in the same way, and in all cases where the solvent containing the alkaloid is run from a separator into a dish for final evaporation, the stem of the separator should be carefully washed. If the solvent solution containing the alkaloid is filtered before evaporation, the filter paper should be thoroughly washed and the stem of the funnel also, and the filter paper should not entirely fill the funnel.

It has been questioned whether it is advisable to put all these details into the text of the assay of every drug, but instead, to describe a typical method in detail and then adapt each drug to it under its own heading. Future compilers will some day settle this point, but no method is too long to read and digest if correct results are desired, and a method is worthless unless it gives a correct valuation of the drug.

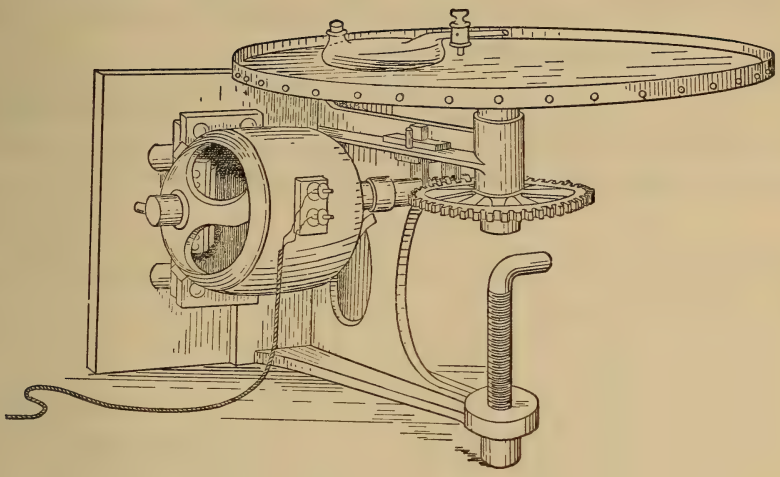
The apparatus required in drug assaying will include a stock of separatory funnels with stopcocks and stoppers carefully and evenly ground to fit tightly and not stick, the most convenient being those of the 4-oz. Squibb type, with several extra of the small and larger sizes. To support these when in the works one of the simplest and most efficient arrangements consists of a number of vertical iron rods bolted about 6 in. apart onto a wooden platform, fitted with a set of ordinary rings and clamps, the rings being of different sizes to accommodate different-size separators, and cut in the circumference directly opposite the clamp. By covering the metal with ordinary Bunsen burner tubing, a firm and safe resting place is provided for the separators.

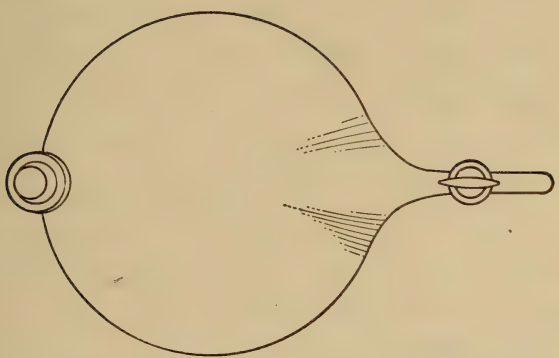
The evaporation of the solvent containing the alkaloid is conveniently carried out in beakers of 100–150 mils capacity. They are small enough to tare and yet large enough to hold any volume of solvent containing the final shake out of an assay.

The maceration and shaking of the ground drug before introduction into the percolator can be conducted to advantage in an 8-oz. nursing bottle. The glass is hard and a stopper can be inserted firmly into the neck and rendered practically immovable by tying.

Percolators of glass for this class of work are now obtainable from apparatus supply houses.

Maceration and shaking out of the ground drug is best accomplished by means of a mechanical shaker, the details of which are apparent from the accompanying diagram. This apparatus should be constructed so that it may be tipped on its side and the disk inclined at an angle, for in certain extraction methods later in the work, where one is handling mixtures prone to emulsify, a turtle-shaped separatory funnel is necessary, thus giving a large surface of contact. When at rest this form of separator

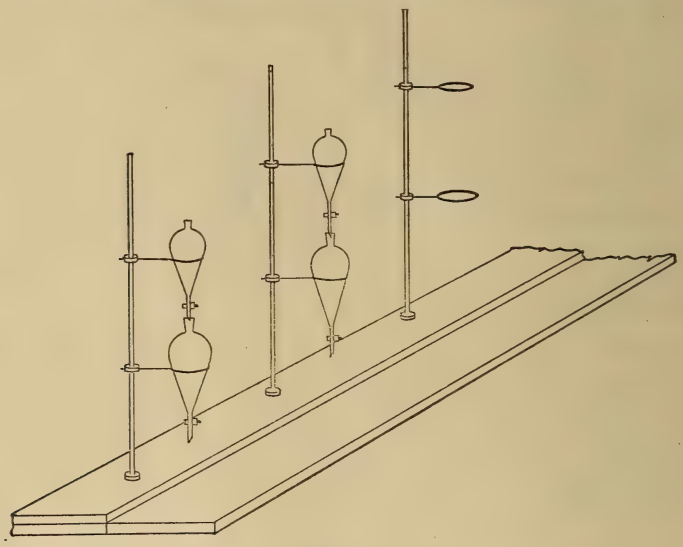




One-way cock

is held in an upright position by a frame consisting of a board back with two screws set perpendicularly to the plane of the board and which can be turned sufficiently to tightly but securely clamp the separator.

For many years cochineal has been a favorite indicator for alkaloidal titration, but the introduction of methyl red, which is now easily obtainable from chemical supply houses, has largely superseded cochineal and is to be preferred.



ACONITE

The assay of this drug has always been a matter of controversy. There are two points to be considered—whether it is a question of reporting the total content of basic principles or to ascertain only the therapeutic activity. Aconitin (ethyl-benzoyl aconin), benzoyl aconin, and aconin are the principal basic components of commercial aconite, and whether the alkaloidal content was wholly aconitin in the fresh drug is a subject yet to be determined; the drug assayist meets with a mixture of bases and the proportions vary. It is apparent that the therapeutic efficiency is due almost solely to the aconitin, and as yet there has been no satisfactory chemical method evolved for determining this body in a mixture of its degradation products. Taylor[1] has studied the different problems connected with assaying aconite from the viewpoint of determining its actual therapeutic value, and concludes that a chemical method, using ether alone, is the only one of any value for obtaining a measure of the aconitin, and that even the residue from an ether extraction contains other basic

[1] J. Ind. Eng. Chem., 1, 1909, 549.

principles in greater or less part but never constant; thus the determination of the total alkaloids is of no value as a measure of the aconitin, and that in order to obtain a true indication of the medicinal value of aconite or any of its preparations the Squibb physiological test should be employed. The latter is in fact very simple and easy of manipulation and gives reliable results after a little practice.

Method of the U. S. P.—Ninth Revision.—The method of the ninth revision is a distinct advance over that in the eighth revision, where the results were neither a measure of the therapeutic activity nor of the basic constituents.

Aconite in No. 40 powder is used and the amounts taken and manipulation of the assay are the same as under Belladonna Leaves, except that ether is used throughout. Each mil of N/50 sulphuric acid consumed corresponds to 12.9 milligrams of ether-soluble alkaloids.

The Squibb Test.[1]—Dilute the fluid extract or the percolate from the ground drug adjusted to fluid extract volume, in such proportion that $\frac{1}{10}$ minim will be contained in 1 fluid dram of water. Rinse out the mouth well to free the surfaces from mucus and saliva and hold the above one dram of dilution in the anterior part of the mouth for exactly one minute and then discharge it. A distinct tingling sensation should be perceived within ten to fifteen minutes.

Taylor says, and my own practice agrees with his, that "the above dilution is in proportion of one part of fluid extract to 600 parts water. In laboratory practice it is better to require the fluid extract of the drug to respond in dilution of 1 in 700, the fluid extract of leaves 1 in 100, the extract of root 1 in 3000, and aconitin 1 in 500,000. In the application of the test, dilute 10 mils of the fluid or 1 gram of the extract to the calculated volume, using water acidulated with acetic acid in the first step and pure water for the final dilution."

ANHALONIUM

The Mescale button contains a number of well-defined alkaloids, and the drug has some use in medicine. To determine the total alkaloids, 5 grams of the powdered drug or 5 mils of the extract evaporated on sawdust are well shaken with 150 mils Prolius mixture (ether 4, chloroform 1, alcohol 1) and 4 mils ammonia water; 50 mils of the solvent are filtered into a separator and exhausted with 2 per cent hydrochloric acid, the latter is then washed with petroleum ether, which is discarded, and then made alkaline with ammonia and extracted with ether-chloroform 1–1. The solvent is filtered into a tared dish, evaporated, dried, and weighed.

[1] Ephemeris 1, 126 and 3, 293.

ASPIDOSPERMA

While this drug does not have an extended use in medicine it contains well-defined bases, and an assay of the total alkaloidal content is not difficult. Twenty grams of the ground drug or 20 mils of the extract evaporated on sawdust are treated in a flask or bottle with 150 mils of petroleum ether-chloroform 2–1 and 4 mils ammonia, and thoroughly shaken; 75 mils of the clear liquid are filtered into a separator and shaken out with 2 per cent hydrochloric acid, the acid solution is washed once with petroleum ether which is discarded and then made alkaline with ammonia and shaken out with ether. The solvent is separated and filtered into a tared dish, evaporated and the residue dried at 100° C. and weighed.

BELLADONNA

The method of the U. S. Pharmacopœia, eighth revision, for this drug is in the main very satisfactory, and gives more accurate information as to the true alkaloidal content of the drug than the method of the ninth revision. It is essential that the acid shake-out should be washed with the ether-chloroform mixture before adding ammonia, and the final chloroform solution should be run through cotton lightly plugged into the stem of the separator when the alkaloidal residue will be in much better shape for titration.

U. S. P., Eighth Revision.—Place ten grams of Belladonna leaves or root in No. 60 powder in an Erlenmeyer flask, and add 50 mils of a mixture of chloroform 1 part and ether 4 parts (both by volume) After inserting the stopper securely allow the flask to stand ten minutes, then add 2 mils of ammonia water mixed with 3 mils of distilled water, and shake the flask well at frequent intervals during one hour. Then transfer as much as possible of the contents of the flask to a small percolator which has been provided with a pledget of cotton packed firmly in the neck and inserted in a separator containing 6 mils of normal sulphuric acid V. S. diluted with 20 mils of distilled water. When the liquid has passed through the cotton, pack the Belladonna leaves firmly in the percolator with the aid of a glass rod, and having rinsed the flask with 10 mils of the chloroform-ether mixture, transfer the remaining contents of the flask to the percolator, by the aid of several small portions (5 mils) of the chloroform-ether mixture, and continue the percolation with successive small portions of the same liquid (using in all 50 mils). Next, shake the separator well for one minute, after securely inserting the stopper, and when the liquids have completely separated, draw off the acid solution into another separator. Add to the chloroform-ether mixture 10 mils of sulphuric acid mixture of the same strength as that previously used, agitate well, and again draw off the acid solution into the second separator; repeat

this operation once more, drawing off the acid solution as before; introduce into the acid solutions contained in the second separator a small piece of red litmus paper, then add ammonia water until the liquid is distinctly alkaline, and shake out with three successive portions of chloroform 15, 15, and 5 mils; collect the chloroform solutions in a beaker, place it on a water-bath containing warm water, and allow the chloroform to evaporate entirely. Dissolve the residue in 3 mils of ether, and let this also evaporate completely. To the alkaloidal residue add 3 mils of N/10 sulphuric acid V. S. and 5 drops of cochineal T. S. (or iodeosin T. S.), then titrate the excess of acid with N/50 potassium hydroxide V. S. Divide the number of mils of N/50 potassium hydroxide V. S. used, by 5, subtract the quotient from 3 (the 3 mils of N/10 sulphuric acid V. S. taken) and multiply the remainder by 0.0287 and this product by 10; the result will be the percentage of total mydriatic alkaloids contained in the Belladonna leaves, or root.

U. S. P., Ninth Revision.—Introduce 15 grams of Belladonna leaves or root in No. 60 powder into a flask of 250 mils capacity and add 150 mils of a mixture of chloroform 1 volume and ether 2 volumes. Stopper the flask, shake it well and allow it to stand ten minutes, then add 5 mils ammonia water and shake vigorously every ten minutes during two hours; now add 15 mils distilled water (25 mils in case of leaf), again shake the flask well and when the drug has settled, decant 100 mils of the solution, representing 10 grams of the drug.

Filter the solution through a pledget of cotton wool into a separator and rinse the graduate and cotton with a little ether. Completely extract the alkaloids from the chloroform-ether solution by shaking out repeatedly with weak sulphuric acid. Collect the acid washings in a separator, add ammonia water until the solution is distinctly alkaline and completely extract the alkaloids by shaking out repeatedly with chloroform. Evaporate the combined chloroform washings to dryness (in case of leaf treat twice with 5 mils ether), add exactly 5 mils of N/10 sulphuric acid to the residue and titrate the excess of acid with N/50 potassium hydroxide using cochineal T. S. as indicator. Each mil of N/10 sulphuric acid consumed corresponds to 28.2 milligrams of total alkaloids.

Javallier[1] has studied the compound of atropin with silicotungstic acid and recommended a method for assaying belladonna and its extracts. The solution of the alkaloid should not be too dilute, as the precipitate is not completely insoluble in water. Hydrochloric acid is added to the solution in such quantity that 2 per cent of free acid is present, and then a 10 per cent solution of silicotungstic acid or its potassium salt is added drop by drop, with stirring; excess of the reagent must be avoided. After standing for twenty-four hours the precipitate is separated by filtration

[1] Bull. Sci. Pharmacol., 1910, 17, 629–34.

or in a centrifugal apparatus, washed with 1 per cent hydrochloric acid, and incinerated. The weight, multiplied by 0.4064, gives the quantity of atropin, to which 0.0048 gram for each 100 mils of the original solution is added as a correction for the solubility of the atropin silicotungstate (the solubility in the wash water may be disregarded). Precipitation may be effected in hot or cold solutions, but prolonged boiling must be avoided. The method can be used for the determination of atropine in belladonna extract.

CANNABIS SATIVA

U. S. P., Ninth Revision.—The method consists of ascertaining the dose of the preparation to be tested which will produce symptoms of incoordination in dogs and then adjusting its strength by comparison with a standard preparation.

Dogs.—The animals differ considerably in susceptibility to the drug and therefore it is best to make preliminary tests upon several dogs with average-sized doses and select from among them the animals which react easily to the drug. As a rule, fox terriers serve very well for the purpose, but any dog may prove satisfactory. It is best to provide at least two dogs for each assay, but if many samples are to be examined more dogs will be needed. The dogs should be at least one year old and in normal health and must be kept under the best sanitary conditions. They may be used repeatedly for the purpose but not at shorter intervals than three days. Each series of tests should be conducted by the same person, who should be perfectly familiar with the peculiarities of each animal in order that he may recognize more certainly deviations from the normal. While the tests are being made the animals should be kept in a perfectly quiet room, free from disturbance and separated so that they cannot see each other.

Preparation of the Drug.—The drug may be given most conveniently in the form of the fluid extract, which is administered in gelatin capsules, or the extract made into soft pills may be used; but whichever form is chosen the same should be used for both the standard and the preparation that is to be tested.

Before administration the animal should not be fed for twenty-four hours in order to hasten absorption. The head of the animal being held, its mouth is opened and the capsule or pill is placed upon the back of the tongue. Usually the drug is easily swallowed when given in this way, but this may be facilitated by giving the animal a small amount of water to drink.

Assay.—An average dose of the known or standard preparation is given to one of the dogs and a like dose of the preparation to be standard-

ized is given the second dog. After one hour both dogs are observed very carefully for symptoms of muscular incoordination. The incoordination is manifested differently in different animals, but in small doses it shows itself most frequently in slight swaying, when the animal is standing quietly, or in some ataxia when it runs about. The observation should be made frequently during the second hour following the administration of the drug.

The results obtained from the first test should be confirmed after an interval of not less than three days by repeating the administration but reversing the order, that is, giving the known strength drug to the dog which received that of unknown strength before and vice versa.

In subsequent tests which are carried out, the dose of the preparation of unknown strength is modified so as to produce similar symptoms to those produced by the standard. If the preparation to be tested is below the standard in strength, its dose must be increased, or if it is above strength its dose is lessened until equivalent doses of the two are found. Dogs may be used over long periods of time, even for some years, but occasionally they have to be discarded, as in some cases they seem to learn the effects of the drug and so refuse to stand up. A certain degree of tolerance is sometimes gained which necessitates larger doses.

Standard.—As there is no chemical substance of definite composition which can be adopted as a standard, a fluid extract of Cannabis or an extract which has been carefully prepared and suitably preserved may be utilized for this purpose. A standard fluid extract will produce incoordination when administered to dogs in the dose of 0.03 mil for each kilogram of body weight of dog. When administered in the form of the extract a dose of 0.004 gram for each kilogram of body weight of dog should produce similar symptoms, and the requirement for a standard tincture is a dose of 0.3 mil for each kilogram of body weight of dog.

CANTHARIDES

Cantharidin occurs partly free and partly combined in several different species of beetles. Many assay methods have been proposed for its determination, and a comparative study of the different methods was made by Kneip, Ney and Reimers.[1] These authors then developed three new procedures, the essentials of which are as follows:

(1) Powdered cantharides is extracted with chloroform in the presence of nitric acid, the solvent carefully evaporated, the residue washed with petroleum ether, then with ether and alcohol saturated with cantharidin, then dissolved in chloroform, the solvent evaporated and dried at 60° C. for one hour.

[1] Arch. Pharm., 249, 259–85.

(2) Powdered cantharides is treated with a weighed amount of chloroform in presence of hydrochloric acid, an aliquot is filtered, evaporated, the residue treated with petroleum ether for twenty-four hours, then washed with more petroleum ether, then with a very weak solution of ammonium carbonate, and finally water; it is then dried at 40° C.

(3) The powder is treated with alcoholic hydrochloric acid for one-quarter hour and after evaporation of the acid, treated in a Soxhlet with a mixture of petroleum ether and benzol 3–5; the solvent is evaporated, the residue washed with a mixture of petroleum ether and alcohol 1–9 and dried at 60° C.

The German Pharmacopœia describes a method for the assay of cantharides, the essentials of which are the same as the second manipulation above mentioned. The purification is, however, carried to greater length; after washing with ammonium carbonate the residue, which is still resinous or dark in color, is extracted with hot acetone which removes the cantharidin.

The Assay of Cantharides (Leger.)[1]—Into a wide mouth flask which can be closed with a pledget of cotton place 25 grams of powdered cantharides, 125 mils benzol, and 2 mils of HCl. Close the flask and keep at 60° or 65° in an oven for three hours with occasional agitation. Let cool and turn the contents of the flask into a displacement apparatus or into a percolator. Close below with cotton, wet with benzol and collect the issuing liquid into a flask and set this fraction (1) aside. Continue the percolation to exhaustion, receiving the product (2) in another flask. The benzol extracts are distilled on a water-bath, beginning with fraction (2) and using a tared flask. When distillation ceases the last traces of benzol are removed by a current of air through the warm flask. After cooling add to the residue in the flask consisting of a green oil in which float crystals of cantharidin, 10 mils of petroleum ether which distills entirely below 50°. Plug the flask and let stand twelve hours. Decant the liquid upon a 7-cm. filter paper which has been tared after drying at 60° or 65° C. and previously moistened with benzol. Retain the crystals as much as possible in the flask, wash them with 24 mils petroleum ether in four portions, which in turn being poured upon a filter is finally thoroughly washed with petroleum ether; dry in the air a few monents and then place both filter and flask in an oven at 60° or 65°, keeping the flask inclined. Weigh at the end of one hour. The amount of cantharidin should not be less than 40 per cent. The use of petroleum ether of low boiling-point permits the drying of the cantharidin at a temperature of 60° or 65°, which minimizes the loss by volatilization. Moreover it is important to incline the flask while in the oven so as to facilitate the cir-

[1] Schweiz. Wochenschr., 1903, 374; Jour. de Phar. et Chim., 1903, 457.

culation of the gases in its interior. Finally the time in the stove is limited to one hour, which is sufficient for desiccation.

CARDIAC STIMULANT DRUGS

The drugs falling under this designation include Apocynum, Convallaria, Digitalis, Squills, Strophanthus and Epinephrin (Adrenalin.) Their physiological activity is best ascertained by means of biochemic tests, which, in many instances, require special apparatus and knowledge of pharmacological technique. The Pharmacopœia method of assaying Digitalis, Squills and Strophanthus has been described under "Digitalis," and for the details of other methods the reader is referred to "Biochemic Drug Assay Methods" by P. S. Pittenger.

Convallaria and Apocynum can be assayed by the Digitalis method, but the characteristic effects of Epinephrin and products of the suprarenal glands are best observed by the change in blood pressure due to intravenous injections.

CINCHONA

Cinchona bark is assayed for its content of total alkaloids, ether soluble alkaloids, and approximate amount of quinin. The ether soluble alkaloids are usually stated to consist of quinin, quinidin, and cinchonidin, but the figures reported often mean but little, as there are other basic substances in cinchona which dissolve in ether and the temperature at which the ether extraction is made, determines the amount of material dissolved. It has been the experience of the author that when using ether it was possible by varying the temperature of extraction to obtain almost any percentage up to that of total alkaloids.

U. S. P., Ninth Revision Method.—The new method differs materially from that in the 8th revision; no attempt is made to distinguish between total and ether-soluble alkaloids, and while the previous method depended on total extraction, which was by no means complete, the new assay is an aliquot process.

Introduce 5 grams of Cinchona, in No. 40 powder, into a 500-mil flask and add 200 mils of a mixture of chloroform, 1 volume, and ether, 2 volumes. Stopper the flask, shake it well, and let it stand ten minutes. Then add 5 mils of ammonia water, shake the flask frequently for one hour, and let it stand from eight to ten hours. Now add 10 mils of distilled water, shake the mixture vigorously, and when the drug has settled, decant 160 mils of the solution, representing 4 grams of Cinchona. Filter it through a pledget of purified cotton into a separator, and rinse both cylinder and cotton with ether. Completely extract the alkaloids from the chloroform-ether solution by shaking out repeatedly with weak sul-

phuric acid. Collect the acid solutions in a separator, add ammonia water until the solution is distinctly alkaline to litmus, and completely extract the alkaloids by shaking out repeatedly with chloroform. Filter each portion of chloroform as it comes from the separator through a pledget of purified cotton into a tared flask, and wash the funnel and cotton with chloroform. Evaporate the chloroform on a water-bath, add 5 mils of alcohol to the residue, and again evaporate. Repeat the evaporation with alcohol and dry the residue at 100° C. to constant weight. The weight will be the amount of total alkaloids from 4 grams of Cinchona.

A modification of Keller's method, made by Fromme, and improved by Engelhardt and Jones[1] is as follows: 2.5 grams of fine or moderately coarse powder are heated in a 200-mil flask with 2 mils of 25 per cent hydrochloric acid and 20 mils of distilled water for ten minutes on a steam bath; the flask is allowed to cool, and then 50 grams of ether and 25 grams of chloroform are added. The mixture is well shaken, supersaturated with 5 mils of caustic potash solution (15 per cent) and then shaken continuously for fifteen minutes; 1.5 grams of gum tragacanth are now added and the mixture shaken again. After the liquids have separated, 60 grams (equal to 2 grams of bark) are filtered, and extracted three times with 1 per cent hydrochloric acid, using 20, 10, and 10 mils respectively. The combined acid solutions are shaken well with 15 mils of chloroform, supersaturated with ammonia, and again well shaken. After settling, the chloroform is filtered through a double filter into a tared Erlenmeyer flask of 100 mils capacity, the aqueous solution shaken twice more with 10 mils of chloroform, the additional chloroform filtered and added to the first. The solvent is then evaporated off and the residue dried at 100° C. to a constant weight. The result is too high, owing to the presence of fatty matter. The residue is therefore dissolved in 10 mils of alcohol and 10 mils of ether, when 30 mils of water are added; the solution is colored with a few drops of hæmatoxylin solution, and N/10 sulphuric acid added with constant shaking until the purple color has almost changed to yellow; 10 mils of water and more acid are now added until a lemon yellow is obtained; then 30 mils of water are added, and, after vigorous shaking, more acid is added until the lemon yellow color persists. Each mil of acid corresponds to 0.0039 gram of total Cinchona alkaloids. The relation of the percentages of the four principal alkaloids of the drug is almost constant.

For the determination of the actual quinin in a bark, Duncan[2] has shown that sodium sulphate will salt out the quinin sulphate from the mixed alkaloids if the solution is kept below 30° C. for twenty-four hours. The quinin should be present in the proportion of .1 gram to 100 mils. The sulphuric acid solution of the mixed alkaloids is exactly neutralized

[1] Pharm. J., 1910, 84, 236. [2] Pharm. J., 1909, 82, 429–30.

with sodium hydroxide solution and 10 grams sodium sulphate added per 100 mils. After twenty-four hours the quinin sulphate is filtered off and either washed with water saturated with quinin sulphate dried and weighed, or with alcohol containing 10 per cent sodium sulphate and titrated with N/20 alcoholic sodium hydroxide using phenolphthalein.

Cohen[1] claims that by the above procedure pure quinin sulphate is not precipitated, and that even after purifying by a second precipitation the losses are much greater than with pure quinin. But whatever the merits of the controversy, the process is of value in aiding the chemist to obtain at least a good approximation of the quinin value of a bark.

COCA

DeJong,[2] who has probably given more attention than anyone else to the study of coca assay during the past few years, perfected a method which was published in 1908; 12.5 grams of finely powdered leaves are mixed with 5 mils of 25 per cent ammonia and the mixture extracted in a Soxhlet apparatus with light petroleum for ten to fifteen hours. After transferring the extract to a stoppered funnel and washing out the flask with light petroleum, the leaves are extracted again for three hours and the light petroleum tested by shaking it with 2 or 3 mils of dilute hydrochloric acid, the acid should not give a turbidity with ammonia. The alkaloidal extract is now shaken with 50 mils and then with 25 mils of dilute (0.5 per cent) hydrochloric acid. When an emulsion is formed, this is transferred to a flask and the liquids separated by a current of air. The acid solution is then filtered through a small filter previously washed twice with water. The filtrate is shaken once with ether (which is set aside) and rendered alkaline with ammonia. It is then shaken first with 50 and then with 25 mils of ether, the ethereal solution allowed to stand for a few minutes, transferred to a tared flask (care being taken not to pour in any drops of water), the flask washed twice with a few mils of ether, which are added to the bulk, the solution evaporated, and the flask heated several times in boiling water; after each heating a current of air is passed through. The flask is finally dried in a desiccator and weighed.

Bierling, Pape, and Vierhover[3] made an exhaustive study of all the known methods of coca assay and conclude that the following procedures give the most reliable results: 10 grams of the air-dried, powdered leaves of known moisture content, are mixed with 4–5 mils of 30 per cent ammonia, and extracted with ether in a Soxhlet apparatus for four to five

[1] Pharm. J., 1909, 82, 670.
[2] Rev. Trav. chim. Pays-Bas, 1908, 27, 419–21.
[3] Arch. Pharm., 1910, 248, 303–36.

hours. A few drops of the ether flowing from the drug should then give no reaction with Mayer's reagent. Or, 12 grams of the powdered leaves in a similar condition are put into a 200-mil flask with 120 grams of ether and 6 mils of 10 per cent, or 3–4 mils of 30 per cent ammonia, and shaken vigorously and repeatedly for half an hour. The liquid is filtered till 100 grams of filtrate are obtained, care being taken to avoid loss by evaporation. The ethereal extract, obtained by either method, is shaken successively with 30, 10, and 10 mils of 2 per cent hydrochloric acid. The last extract should give no reaction with Mayer's reagent. The acid extracts are filtered if necessary, and shaken out once with ether, if colored yellow. The extract is made alkaline with ammonia, and shaken with 40–50 mils of either till the aqueous portion is colorless or no longer turbid. The aqueous liquid is shaken twice more with 20 mils of ether. The ethereal solution is placed in a tared flask and the ether distilled off. The residue after being treated twice with 5 mils of ether, which is driven off each time by means of a current of dry air, is dried at 100° C. till of constant weight. It is dissolved in a little ether, treated with 5 mils of N/10 hydrochloric acid, and warmed to remove the ether. The excess of acid may then be titrated with caustic soda, after the addition of 10 drops of a fresh 1 per cent hæmatoxylin solution and 40–50 mils of water, or after the addition of 5 drops of iodeosin solution and some ether. If preferred the alkaloidal residue can be dissolved in 3–5 mils of absolute alcohol and titrated with N/10 hydrochloric acid, using two drops of 0.5 per cent methyl red as indicator.

1 mil N/10 acid = 30.318 mg. cocain

COLCHICUM

Dohme, Engelhardt and Schmidt[1] have shown that the colchicin obtained in the assay of the corm by the U. S. P. Method, 8th revision, is 35–48 per cent pure and the seed 58–75 per cent. The old assay was replete with faults and was foreordained to give erroneous results.

The new method for assaying Colchicum seed is as follows: Introduce 15 grams of Colchicum Seed, in No. 60 powder, into a 500-mil flask, and add 10 mils of solution of lead subacetate and 290 mils of distilled water. Weigh the flask and contents, and digest the mixture at from 60° to 70° C. for three hours, with occasional agitation. Cool, add distilled water to restore the original weight, and filter off 200 mils. Add 0.75 gram of sodium phosphate to the clear filtrate, shake the mixture frequently during half an hour, and filter off 100 mils, representing 5 grams of Colchicum seed. Shake out the alkaloid from the filtrate with chloroform until com-

[1] Druggists' Circular, 1910, 58.

pletely extracted, as shown by testing with iodine T. S. (in place of the usual mercuric potassium iodid T. S.), and evaporate the chloroform solution; add about one mil of alcohol and again evaporate. Repeat this operation once more and dry the residue to constant weight at 100° C. To this weighed residue contained in a flask add 5 mils of N/10 sulphuric acid V. S. and 5 mils of distilled water and heat the mixture for ten minutes at 70° C. Now filter the liquid through a pledget of purified cotton, wash the flask and cotton with distilled water, reject the filtrate and washings and remove as much of the water from the cotton as possible. Dissolve any insoluble residue that may remain on the cotton by washing it first with a little alcohol and then with ether; collect the alcohol-ether washings in the flask, evaporate, and dry the residue to constant weight at 100° C. Deduct this weight from the weight of residue previously obtained. The difference will be the weight of colchicin obtained from 5 grams of Colchicum seed.

There have been many methods proposed for the analysis of Colchicum, but all have failed to give a pure colchicin. Farr and Wright[1] seem to have made the greatest advance by recommending the purification of the crude colchicin with iodine and their method as a whole is especially commendable. Five grams of the powdered drug are packed in a percolator of 2 cm. diameter and exhausted by slow percolation with 50 per cent alcohol. The percolate is evaporated in a porcelain dish with 25 mils water on the water-bath till the volume is reduced to 20 mils. The warm liquid is transferred to a separator and the dish rinsed with a little water and 25 mils of light petroleum ether. The aqueous solution is shaken with 20, 10, and 5 mils chloroform, the extraction being repeated as long as any alkaloid is extracted. The chloroform is distilled off and the residue treated with a mixture of 19 mils water and 1 mil ammonia, used in four portions, then with a mixture of 16 mils water and 4 mils dilute sulphuric acid. These solutions are now all filtered into a flask, the acid being in excess, 20 mils of iodine test solution added and the precipitate filtered off. The flask and precipitate are washed out with 20 mils of water containing 1 mil each of sulphuric acid and iodine (as the alkaloidal iodides are unstable in the presence of water it would be safer to wash out the flask with test solution alone). The filter and contents are ground to a pulp with 20 mils sodium thiosulphate and 2 mils sodium carbonate test solutions, the mixture filtered through cotton into a separator, and the solid matter washed with water until it gives no precipitate with iodine. The filtrate and washings are shaken out with chloroform, the solvent evaporated at a low temperature and the residue dissolved in 90 per cent alcohol, evaporated, and dried to constant weight at 100° C.

[1] Pharm. J., 1910, 85, 578–80.

CONIUM

National Formulary Method.—Place 15 grams of Conium, in No. 40 powder, in a 250-mil Erlenmeyer flask, add 150 mils of purified petroleum benzin and then 15 mils of solution of sodium hydroxide, insert the stopper securely, and shake the flask vigorously at frequent intervals during six hours. Allow the mixture to settle and decant 100 mils of the clear benzin solution (representing 10 grams of the drug) into a separator; extract the alkaloid by shaking with successive portions of weak hydrochloric acid until a few drops of the last washing gives no precipitate with iodine T. S. Collect the acid washings and concentrate by evaporation on a water-bath to 10 mils, cool and transfer the liquid to a separator, then cautiously add sodium carbonate in excess. Extract the alkaloid by shaking out with successive portions of 15 mils each of purified petroleum benzin. Separate the benzin washings and filter into a beaker. Then add exactly 10 mils of N/10 sulphuric acid V. S. and stir thoroughly for two minutes so as to mix the acid and benzin solution. Evaporate the benzin layer in a current of warm air, at a temperature not exceeding 60° C., and as soon as the benzin has disappeared, cool, add 5 drops of cochineal T. S. or methyl red T. S. and titrate the acid solution with N/50 potassium hydroxide V. S. Each mil of N/10 sulphuric acid V. S. consumed corresponds to 0.0126 gram of coniin. Calculate the amount of coniin neutralized by the acid, and multiply the result by ten to obtain the percentage of coniin in the drug.

Squires method for the assay of conium and its preparations is as follows: 5 grams of the finely powdered drug or its equivalent of fluid extract or tincture evaporated on sawdust is extracted with 50 mils of chloroform saturated with hydrogen chloride, the extraction with a smaller quantity of the solvent being repeated until 6 drops on evaporation give no precipitate with Mayer's reagent and dilute-sulphuric acid. The total chloroformic extract is shaken out twice with 25-mil portions of water, and the latter washed twice with 10-mil portions of chloroform, which is discarded. The aqueous solution is made alkaline with sodium hydroxide and the coniin shaken out with 3 portions of chloroform; to the latter is added 10 mils of chloroform saturated with hydrogen chloride and the whole evaporated, dried at 90° C. and weighed; 162.4 parts of anhydrous coniin hydrochloride equals 126.2 parts of coniin.

A simple volumetric titration method consists in treating 10 grams of the finely powdered drug or 10 mils of the fluid extract with 50 mils petroleum ether and 5 mils of hydrochloric acid 10 per cent and thoroughly shaking. This operation is repeated, and then the drug is treated with 80 mils of petroleum ether and sufficient potassium carbonate to render the mixture alkaline. After a thorough shaking the mixture is allowed

to stand overnight. Forty mils are then filtered into a titration flask, 10 mils N/10 sulphuric acid are added, the petroleum ether evaporated at a gentle heat, and the excess of acid titrated with N/50 alkali.

1 mil N/50 H_2SO_4 = .002543 gram coniin.

DIGITALIS

With Digitalis as well as with other drugs of the heart-tonic class the physiological assay seems to be the best measure of its therapeutic activity. The assays in general use include the minimum lethal dose method; Focke's method where the potency is assumed to be directly proportional to the weight of the frog and inversely to the dose and time, the value of the preparation being determined by the equation $V = pdt$; and the determination of the amount of digitoxin by chemical means. Each physiological method has its own ardent supporters, and there is much controversy as to which is the best, but there are so many factors entering into animal experimentation that no attempt will be made to offer any opinion as to which method is the best.

Schmiedeberg[1] has emphasized the unreliability of all methods for determining the activity of digitalis, and concludes that the relative activity of different lots of leaves can be determined with sufficient accuracy as follows: the heart of Rana temporaria is exposed and connected with the Williams' frog heart apparatus and perfused with 2 parts 0.7 per cent sodium chloride solution and 1 part ox blood, to which the substance is added. The time is noted from the beginning of the poisoning till the cessation of the heart beats. Care must be taken that all the tests are made under as nearly identical conditions as possible, by the use of the same concentration of the leaf infusion, maintenance of constant concentration during perfusion, and the employment of healthy male hearts. The infusion is made by 70 mils boiling water on 1 gram powdered leaves, shaking for five minutes, filtering and washing with hot water to a volume of 100 mils; 95 per cent of the active principles are removed in this manner. The activity of the extracts of each lot is compared with that of strophanthin. It was found that there was no direct way of comparing the activity of any one extract with that of strophanthin, as only those quantities could be compared that produced the same effect in the same time. But the value of the extract can be compared with the activity of a certain amount of strophanthin calculated by interpolation in a series of results obtained with different amounts of strophanthin and so the extracts of several lots of leaves can be compared with one another.

[1] Arch. exp. path. Pharm., 62, 305–28.

Physiological methods for Assay of Digitalis

U. S. P., Ninth Revision.—After the frogs have been weighed, the doses to be given are calculated according to their weights and are measured into small conical glasses by means of a finely graduated pipette. The doses of the preparation which are to be injected should be as uniform in quantity as possible and should not exceed 0.015 mil for each gram of body weight of frog. The members of the digitalis series may be assayed in either fluid extract or tincture strength, being diluted with water as may be necessary to get the volume dose. In case the alcohol content in any preparation after dilution is higher than 20 per cent the preparation may be subjected to careful evaporation and subsequent dilution with an aqueous solution containing 0.7 per cent of sodium chloride until the original volume is restored and the alcohol content is not above the per cent named. It is always best to have the alcohol content of different preparations uniform. In case there is a precipitate the preparation to be assayed should be shaken each time a dose is measured out.

When the doses are ready, they may be injected into the anterior lymph sac of the animal. This is done by means of a glass pipette which is drawn out to a fine point. The frog is held on its back in one hand and the pipette with the contained drug in the other, the mouth of the frog is opened with the point of the pipette and, carefully avoiding the tongue, the floor of the mouth is punctured and the point of the pipette is then seen to enter the anterior lymph sac of the frog. The contents of the pipette are now forced into the sac either by gravity or by gently blowing if necessary. In the latter case, care should be taken not to introduce air into the sac. Care should also be taken not to puncture the skin. The animal is then replaced in its cage in the tank, the temperature of which is maintained as stated at 20° C.

At the end of one hour from the time of injection each frog is pithed, both brain and cord, the heart is exposed and its condition examined. For the correct end reaction the ventricle should be in systolic standstill while the auricles should be widely dilated.

Following mechanical stimulation feeble contractions may be allowed in the auricles and localized contractions in the ventricle, but no general contraction is allowable.

If when the heart of an animal is being exposed for examination, remains of the injected drug are found in the lymph sac unabsorbed, such an animal should be discarded and not considered in the results obtained.

It happens sometimes that one frog out of a large series may prove a decided exception to the others in the way of increased or decreased susceptibility to the drug. Such an animal should also be discarded.

After the primary or trial assay has been carried out and the approximate strength of the preparation ascertained, a second series of frogs is

injected in like manner, using doses the limits of which are considerably narrower than the first series. A third or even fourth series of injections may be necessary to confirm the earlier results. The dose thus found is then compared with the dose of a standard which is similarly ascertained upon another series of frogs of the same lot. From such a comparison the strength of the unknown preparation can be suitably adjusted.

The use of a standard is made necessary by the fact that frogs differ in their susceptibility to the members of the digitalis series at different seasons of the year. The condition of susceptibility is ascertained and allowed for by the use of a solution of ouabain as a standard which in appropriate doses is injected into a series of frogs and their resistance thus determined. The necessary strength of an unknown preparation may be calculated from the dose actually found by the ratio of the standard dose of ouabain to the dose of ouabain found necessary to kill. Thus:

Standard dose of ouabain	:	Found dose of ouabain	::	Standard dose of drug being assayed	:	Necessary dose of unknown.

The standard dose of ouabain is 0.0000005 gram per gram of body weight of frog.

The standard dose of Tincture of Digitalis to correspond is 0.006 mil per gram of body weight of frog.

If, therefore, in a certain series of frogs the resistance to ouabain is found to be increased so that a dose of 0.00000075 gram is necessary to stop the heart in systole in one hour, the dose of Tincture of Digitalis would also have to be increased to 0.009 mil, and the actual dose found calculated against this, instead of against the standard dose of 0.006 mil. For example, in frogs showing the increased resistance as indicated above if the Tincture being examined assays 0.018 mil per gram of body weight it is one-half strength.

Standards.—The standards adopted are as follows:

	Gram or Mil for Each Gram of Body Weight of Frog.
Standard dose of ouabain	0.0000005
Digitalis:	
Leaves (in the form of tincture)	0.0006
Fluid extract	0.0006
Tincture	0.006
Strophanthus:	
Seed (in the form of tincture)	0.000006
Tincture	0.00006
Squill:	
Dried Squill (in the form of tincture)	0.0006
Fluid extract	0.0006
Tincture	0.006

KELLER'S METHOD FOR THE DETERMINATION OF DIGITOXIN

Twenty-eight grams of air-dried, powdered digitalis leaves are placed in a suitable glass-stoppered flask of 500-mil capacity; over these are poured 280 grams of alcohol 60 per cent (by weight) and the mixture is left to stand for three to four hours, shaking it frequently. It is then filtered and 207 grams of the filtrate are evaporated to about 25 grams on a water-bath. Sufficient water is added to the residue to bring the total weight to 222 grams, and while stirring, 25 grams of official liq. plumbi subacetatis fort. are added. The mixture is immediately filtered and to 132 grams of the filtrate, in an Erlenmeyer flask, a solution of 5 grams of sodium sulphate in 8 grams of water is added. When the precipitate has settled, 130 grams of the clear fluid are poured into a separator, 2 grams of solution of ammonia (10 per cent NH_3) are added and the mixture is shaken five times, each time with 30 mils of chloroform. The chloroformic solutions are filtered and then evaporated, the dry residue is dissolved in 3 grams of chloroform, and, in order to precipitate the digitoxin, 7 grams of ether and 50 grams of petroleum ether are added. The flocculent digitoxin which separates is collected on a small filter (5 cm. diameter) and dissolved on the filter by the addition of hot absolute alcohol. The alcoholic solution which runs through is collected in a glass capsule, evaporated to dryness and the residue dried until the weight is constant. This multiplied by 10 gives the percentage of digitoxin contained in the leaves analyzed.

Vanderkleed[1] recommends a modification of Keller's method of chemical assay in which a determination of the digitoxin gives results in close accordance with the physiological determination of the lethal dose as shown by simultaneous control experiments.

Twenty grams of the powdered leaves are extracted by percolation with 70 per cent alcohol, and the percolate is evaporated on the water-bath until all the alcohol has been driven off. In the case of the tincture 200 mils, or a fluid extract, 20 mils, are similarly treated. The residue is rinsed with sufficient water to bring the volume to 150 mils. Fifteen mils of a 25 per cent solution of lead acetate are then added, and the mixture is diluted to 200 mils. The precipitate is filtered off, thoroughly drained and washed. The filtrate is made up to 200 mils and excess of lead removed by means of sodium sulphate or phosphate. After standing for twenty-four hours, the precipitate is filtered off, drained, and washed. (The taking of aliquot parts, in order to avoid filtrations and washings, cannot be advocated in digitalis assays, on account of the volume of the precipitates.) The filtrate is transferred to a separator, 2 mils of 10 per cent solution of ammonia are added, and the alkaline

[1] Amer. J. Pharm., 1908, 80, 114–20.

liquid is shaken with five successive 30-mil portions of chloroform. The chloroform extract is distilled to dryness in a tared flask on the water-bath; the crude residual digitoxin is redissolved in 3 mils of chloroform; 10 mils of ether and 70 mils of light petroleum spirit are added, and the mixture is allowed to stand in a cold place for twenty-four hours. The digitoxin, in a micro-crystalline form, adheres to the flask, allowing the greater part of the liquid to be decanted. The last few drops are evaporated, and the precipitate is dried, in the flask, at 60° C., and then weighed as digitoxin. The average amount of digitoxin found, in four years, in digitalis leaves is 0.313 per cent; the highest yield is 0.455 per cent; the lowest 0.171 per cent. Four samples of U. S. P. tincture gave from 0.023 to 0.037 per cent; one tincture free from fat yielded 0.027 per cent. Three fluid extracts gave from 0.234 to 0.264 per cent, and the powdered solid extract 1.061 per cent of digitoxin.

ERGOT

Ergot may be assayed by several physiological methods including the cock's-comb method, the blood-pressure method, and uterine method. The latter two require special complicated apparatus and can be handled to advantage only by one skilled in pharmacological practice. The details of the manipulations are ably described in Pittenger's work, "Biochemic Drug Assay Methods." For practical purposes the cocks'-comb method yields good results and is not difficult to carry out. It consists in determining the minimum amount of solution of ergot necessary to cause the same degree of bluing in the cock's comb and wattles as that produced by a given amount of a standard preparation. The best subjects are white Leghorn roosters weighing 1200–1600 grams, and the injections are made deep into the breast muscle, or the preparation to be tested may be introduced into the crop through a soft rubber tube. Pittenger's directions are as follows:

Inject one cock with a dose of the standard preparation. Inject another with the same dose of the unknown preparation, and, one hour after the injections have been given, compare the color of the two combs, as the maximum cyanosis seems to be reached in about that time. The color begins to fade soon after, so that at the end of two hours or more, depending on the amount of drug given, the comb will usually appear to be nearly normal. Judging from the results obtained from the first two injections, the dose of the unknown preparation is increased or diminished until that amount is found which will give approximately the same intensity of action as was shown by the color of the comb of the rooster injected with the standard. The same roosters may be used for several tests, but the injections should be made at intervals of two or three days, so as to allow sufficient time for complete recovery from the

effects of previous administrations of the drug. It should be considered sufficiently accurate if the first injections of the standard and of the unknown preparations produce the same degree of activity, because it is believed that individual variation in different birds might be sufficiently great to interfere. This variation can be reduced to a minimum, if the order of the injection on the succeeding day be reversed until each preparation has been given to each of several birds in turn. The results are then based on the average of the several injections. The final comparisons demand careful selection of the birds to be injected. A choice of two birds of about the same size and which had previously reacted well to the drug is advisable. With a little practice it is easy to compare the intensity of the discoloration in the two cocks' combs and to so regulate the dose of the drug given as to produce approximately the same degree of reaction. The doses thus obtained will give the relative strength of the two drugs.

Variations may further be avoided by using only such roosters as react alike to a standard preparation, and also by constantly changing the order of injections so that the same cock shall not receive the same specimen of the drug twice in succession. Although the relative strength of two preparations may be thus determined quite accurately by this method, it is not well adapted for standardization work, because it requires that a standard preparation shall be kept on hand. This makes the standard dependent upon the keeping qualities of a stock galenical. Any deterioration, therefore, will result in a lowering of the standard for all subsequent preparations. Owing to the rapid deterioration in preparations of ergot, it is, therefore, practically impossible to keep on hand a preparation of standard strength, and it is believed that more satisfactory results may be obtained by the blood-pressure method because the blood-pressure may be accurately measured by the manometer and kymograph and the same permanently recorded. The principal objection to this method, however, is the fact that the personal equation plays an important part in the assay, since the accuracy of the test depends largely upon the experience of the operator and his ability in determining just when the coloration produced by the unknown equals that produced by the standard. In the hands of an experienced operator, however, results may be obtained which will show, with fair accuracy, the relative value of any preparation of ergot.

Standard fluid extracts should be prepared from good quality ergot. These standard products will keep without deterioration if preserved in sealed tubes from which the air has been exhausted. A standard extract will produce a moderate grade of cyanosis in doses of about 1 mil.

Keller-Fromme Method for Determining Cornutin (Ergotinin) in Ergot.—Place 25 grams of finely powdered ergot in a small percolator

closed with a plug of cotton-wool, and slowly extract with petroleum ether until a drop on evaporation does not leave any oily stain on filter paper. The whole of the powder is then removed from the percolator and the petroleum ether allowed to evaporate off before introducing the powder into a bottle with a capacity of about 250 mils. Ether (125 mils) and magnesia mixture (1 gram of light magnesia and 40 grams of water) are then added, and the mixture shaken repeatedly during thirty minutes. Next 3 grams of powdered tragacanth are added, and the mixture well shaken prior to passing 100 grams (or as much as possible) of the ethereal solvent through a plug of cotton-wool in a covered funnel. The liquid (of which each 5 grams represents 1 gram of powder) is next shaken out with 25, 20, and 15 mils of dilute hydrochloric acid (1 per cent) until the acid liquor gives no cloudiness with Mayer's reagent. The bulked acid liquors are shaken up with 0.3 gram of kieselguhr and again filtered, washing the bottle and filter with a little water. The filtrate is then made alkaline with ammonia and shaken out with 25, 10, and 10 mils of ether, the ethereal solution being filtered into a tared Erlenmeyer flask. The solvent is removed by distillation and the residue dried till of constant weight. If 100 grams of ether solution were shaken out, this weight, multiplied by 5, is equal to the percentage of cornutin (ergotinin.)

GELSEMIUM

A simple process consists in treating 20 grams of the powdered drug or 20 mils of the fluid extract evaporated on sawdust, with 150 mils ether and 4 mils ammonia water and thoroughly shaking. Seventy-five mils of the clear liquid are then transferred to a separator and extracted with 5 per cent sulphuric acid, the latter being filtered into another separator and shaken out once with petroleum ether, which is discarded. Ammonia is added in excess and the alkaline liquid shaken out with ether-chloroform 3–1, the latter being filtered into a tared dish, evaporated, dried, and weighed.

Sayre[1] recommends Webster's process, by which 10 mils of the fluid extract are precipitated with 1.5 grams tartaric acid, filtered, and the precipitate washed with alcohol, the filtrate and washings made up to 100 mils and allowed to stand until any further precipitate has settled, and again filtered. One-half of the filtrate (representing 5 mils) is evaporated to dryness and the residue treated with 10 mils N/2 sulphuric acid and filtered into a separator; potassium hydroxide 20 per cent is added in excess and the alkaloids shaken out with chloroform-ether (4–1); the solvent is washed with two portions of water and treated with 20 mils N/100 sulphuric acid, thoroughly shaken and the excess of acid titrated with N/100 alkali, using cochineal.

1 mil N/100 H_2SO_4 = .00408 gram Gelsemium Alkaloids.

[1] Drug. Circ., 1911, 55.

GUARANA

The new aliquot gravimetric method of the U. S. P., Ninth revision, does not give a caffein which can be termed strictly pure. Pure caffein residues cannot be obtained from any drug or caffein-containing substance without an iodine purification.

The method is as follows: Introduce 6 grams of Guarana in No. 60 powder into a flask and add 120 mils chloroform and 6 mils ammonia water. Stopper the flask, shake it frequently for half an hour, then let it stand four hours. Again shake the flask vigorously and when the drug has settled decant 100 mils of the liquid representing 5 grams of Guarana, then filter through a pledget of purified cotton. Evaporate the clear filtrate to dryness and dissolve the residue in weak sulphuric acid with the aid of heat. When the liquid has cooled filter it into a separator and wash the container and filter with several small portions of distilled water. Now add ammonia water until the liquid is distinctly alkaline and completely extract the caffein by repeatedly shaking out with chloroform. Evaporate the united chloroform solution to constant weight at 80° C. and weigh.

HOANG-NAN AND IGNATIA

These two drugs contain strychnin and brucin, and they and their extracts can be assayed by the same methods as obtain with nux vomica.

HYDRASTIS

U. S. P., Ninth Revision Method.—Introduce 10 grams of Hydrastis, in No. 60 powder, into a 250-mil flask and add 100 mils of ether and proceed as directed under "Belladonna," beginning with the word "Stopper." Modify the process there given by using 50 mils of the ether solution, representing 5 grams of Hydrastis, to complete the assay. Use ether instead of chloroform for the final shaking out of the alkaloids, and dry the residue to constant weight at 100° C. instead of titrating. The weight is the amount of ether-soluble alkaloids from 5 grams of Hydrastis.

John Uri Lloyd's Method.—

Very finely powdered Hydrastis (passed through fine bolting cloth)	2 grams
Lloyd's reagent (see page 68)	1 gram
Ammoniated alcohol (not ammonia water)	10 mils } mixed
Chloroform	100 mils } mixed
Glycerin	8 mils
Aqua ammonia, q. s.	
Sulphuric ether	60 mils

Into a stoppered, 8-oz. separator, put 50 mils of the chloroform-ammoniated alcohol mixture. Add the Hydrastis, and shake well together. Next

add the Lloyd's reagent, and shake well together. Then add the glycerin and shake vigorously, until perfect separation of the chloroformic liquid and the resultant magma takes place. Draw off the chloroform solution, filtering through a cottoned separator with 20 mils of the chloroform-ammonia solution, shaking vigorously, as before, and drawing off the clear solution, filtering through the same cottoned funnel as previously used, into the distilling flask. Repeat, with 20 mils of the chloroform-ammonia solution, until this is exhausted (three washings.)

In the process above given, it is essential that no filter paper be employed. Filter through pledget of cotton, previously saturated with the appropriate menstruum. (In this instance, chloroform.)

Connect the flask with a condenser, and (water-bath) distill off the chloroform. The residue will not become dry, by reason of a small portion of glycerin. Wash this residue with diluted sulphuric acid (one-fourth the strength of U. S. P. dilute sulphuric acid), using three successive portions of 10 mils each, and filtering through a cottoned funnel (water-saturated), into an 8-oz. separator. Add ammonia water to slight excess, and abstract with 20 mils sulphuric ether, filtering the ether. Repeat, using two other portions of sulphuric ether, 20 mils each, and evaporate to dryness. Flow over the residue 5 mils cold, distilled water, and decant. This, to remove traces of ammonium sulphate. Dry the residue perfectly, multiply by 100 and divide by 2. The result gives the percentage of pure hydrastin in the drug, in an amorphous form. If the crystalline form is desired, dissolve in a small amount of alcohol, and allow to evaporate spontaneously.

Roeder's[1] method, which is a type of several methods, proposed for determining hydrastin in the extract is as follows:

Six grams of the fluid extract are diluted with about 5 mils of water, and evaporated to drive off the alcohol. After cooling, 2 mils of 20 per cent sulphuric acid are added, the mixture being allowed to stand, with occasional agitation, for from one-half to one hour. Twenty grams of light petroleum spirit and 100 grams of ether are added; after well shaking, sufficient 10 per cent solution of ammonia to give an alkaline reaction (about 5 mils) is run in, and the whole is well shaken for ten to fifteen minutes. After separation, a portion of the ether layer equivalent to 5 grams of the original extract is decanted and shaken with 25, 25, 10, and 10 mils of 0.5 per cent hydrochloric acid, or until a drop of the acid liquid gives no reaction with Mayer's reagent. The united acid extract is filtered into a separator, the alkaloid is liberated with excess of ammonia, and extracted with 50, 30, 10, 10, and 10 mils of ether in succession. The ether solutions are evaporated in a tared vessel, and the residue dried at 100° C., is weighed. In the case of the rhizome, 6 grams of the drug,

[1] Apoth. Zeit., 1908, 23, 583.

in finest powder, are extracted with ether, and the ether residue is treated as above.

Rupp[1] describes a method which is representative of another type of assay: Ten grams of the liquid extract are mixed, in a tared 125-mil Erlenmeyer flask, with 20 grams of water, and evaporated by gentle boiling until the weight is reduced to 9 or 11 grams, in order to drive off the alcohol. After cooling somewhat, 1.5 grams of dilute hydrochloric acid are added, and the total weight is brought up to 20 grams by the addition of more water. One gram of talc is then added, the mixture is strongly shaken for one minute, and thrown on a plain filter. Ten grams of filtrate are collected in a 100-mil flask; 4 grams of solution of ammonia and 20 grams of ether are added and the whole is well shaken for a minute; 20 grams of light petroleum spirit are then added, and thorough agitation is repeated; after a further addition of 1.5 grams of powdered tragacanth, the whole is shaken until the gum aggregates. Thirty-two grams of the clear liquid (=4 grams of the original extract) are then decanted into a tall, tared beaker, the solvent is evaporated off, and the residue of hydrastin dried till of constant weight.

HYOSCYAMUS

The method in the ninth revision U. S. P. is the same as for Belladonna leaves except that 30 grams of drug in No. 60 powder and 300 c.c. of the chloroform-ether mixture are to be used. The amount of distilled water to be added after maceration is increased to 40 mils, and 200 mils of the chloroform-ether solution are taken, representing 20 grams of Hyoscyamus.

IPECAC

The method in the ninth revision U. S. P. is identical with that for Belladonna leaves, with the exception that 10 grams of the drug in No. 80 powder, to 100 mils of ether are used, and 50 mils of the ether solution representing 5 grams of Ipecac taken. Ether only is used, throughout and the residue is dissolved in 10 mils of N/10 sulphuric acid. Each mil of the acid consumed corresponds to 24 milligrams of Ipecac alkaloids.

Patterson[2] gives a method for estimating the emetin and cephaelin in Ipecac which he considers both simple and rapid. Twelve grams of the powdered drug are mixed with 10 mils ammonia water or 10 mils sodium carbonate (1–3) and 120 mils of a mixture of 1 part chloroform, 1 part amyl alcohol, and 3 parts ether. The whole is well shaken for an hour, 10–15 mils water added to aggregate the powder, 100 mils of the liquid decanted and evaporated to one-half if ammonia has been used. It is then shaken out with 15 mils N/10 hydrochloric acid, followed by

[1] Apoth. Zeit., 1909, 24, 922–923. [2] Pharm. J., 1903, 71, 102.

three portions of water 5 mils each, the acid solution treated with excess of N/1 potassium hydroxide and shaken out four times with ether, preserving both aqueous and ethereal solutions. The latter are shaken out three times with N/20 potassium hydroxide, the potash solution washed once with ether and then all the ethereal solutions evaporated and weighed or titrated as emetin. The aqueous solutions are then mixed, acidified with hydrochloric acid, ammonia added in excess and shaken out four or five times with ether-chloroform (1–6), the latter evaporated and the residue weighed or titrated as cephaelin.

JALAP

The U. S. P., ninth revision directs as follows: Pack 10 grams of jalap in No 60 powder in a cylindrical percolator and extract it with alcohol until 100 mils of percolate is obtained. Transfer 20 mils of the percolate to a separator, add 20 mils of chloroform. Mix the liquids, then add 20 mils of distilled water and shake throughly. When the liquids have completely separated, draw off the chloroform into a tared beaker, wash the separator with 5 mils chloroform and add it to the beaker. Evaporate the chloroform solution on a water-bath, add 2 mils of alcohol and again evaporate, dry to constant weight and weigh. The resulting weight will be the amount of total resin obtained.

KOLA

National Formulary Method.—Introduce 6 grams of Kola, in No. 60 powder, into a flask and add 120 mils of chloroform and 6 mils of ammonia water. Stopper the flask, shake it frequently for half an hour, then let it stand four hours. Again shake the flask vigorously and, when the drug has settled, filter the liquid rapidly through a pledget of purified cotton and collect 100 mils of the filtrate, representing 5 grams of kola. Evaporate the clear filtrate to dryness and dissolve the resdue in 5 mils of weak sulphuric acid with the aid of a gentle heat. When the liquid has cooled, filter it into a separator and wash the container and filter with several small portions of distilled water. Now add ammonia water until the liquid is distinctly alkaline to litmus and shake out the alkaloid with successive portions of chloroform until completely extracted, as shown by testing with iodine T. S. Evaporate the united chloroform solutions and dry the residue to constant weight at 80° C. The weight is the amount of caffein from 5 grams of Kola.

Kola yields not more than 3 per cent of ash.

LICORICE

Tschirch has shown that glycyrrhizin on hydrolysis yields two molecules of glucuronic acid, an aldehyde acid which reduces Fehling's solu-

tion, and based on this fact Eriksson [1] has proposed a method for estimating glycyrrhizin both in the extract and the drug. Ten grams of the extract coarsely powdered are treated with 100 mils of cold water and when dissolved 100 mils of 90 per cent alcohol added, heated for one-half hour on the water-bath, filtered, the filter washed with 50 mils of hot alcohol, the filtrate heated on the water-bath until the alcohol is removed, and then made up to 200 mils with water. Forty mils of this solution are treated with 25 per cent sulphuric acid as long as a precipitate is formed, and after standing two to three hours, the glycyrrhizin is filtered off and washed with 5 per cent sulphuric acid. The filter with the glycyrrhizin is heated with 50 mils 90 per cent alcohol, filtered and 30 mils water added to the filtrate. The alcohol is driven off and the glycyrrhizin is reprecipitated with sulphuric acid, filtered, dissolved in 5 per cent sodium hydroxide, diluted with water, and boiled under a reflux for fifteen hours with 120 mils of Fehling's solution. The copper reducing power of the solution is then determined in terms of dextrose and from the amount of the latter the glycyrrhizin is calculated, 360 parts of dextrose being equivalent to 896 parts of glycyrrhizin.

The method may be applied to licorice root. The ground root is extracted with alkaline water, and after precipitating gummy substances with alcohol, the solution is boiled for three to five minutes with excess of Fehling's solution until the reduction due to reducing sugars and hexoses is complete and after filtering from the cuprous oxide, the glycyrrhizin is determined by boiling for fifteen hours with Fehling's solution.

Glycyrrhizin may also be determined gravimetrically: two grams of the extract are dissolved in 30 mils of warm water and to the cool solution 118 mils of 95 per cent alcohol added and the flask allowed to stand twelve hours. The precipitate is then filtered and washed with 75 per cent alcohol and the filtrate evaporated. The residue is dissolved in warm water and precipitated with 10 per cent sulphuric acid, the precipitate is washed with acidulated water and finally with a small quantity of distilled water cooled to 2° C., then dissolved in strong ammonia and the solution evaporated to dryness in a tared dish, dried at 100° C. and the residue weighed as ammonium glycyrrhizinate.

LOBELIA

Lobelin, the alkaloid of Lobelia inflata, may be determined in the tincture by Farr and Wright's method: Fifty mils of the tincture are treated with 5 drops of acetic acid 33 per cent and 20-30 mils of water and evaporated on the water-bath to about 30 mils. The liquid is filtered through cotton into a separator and the dish and cotton washed with

[1] Arch. Pharm., 1911, 249, 144-60.

acidified water. Ammonia is then added in excess and the liberated alkaloid shaken out three times with a little chloroform, the solvent is evaporated at a gentle heat, and the residue treated twice with 5 mils of hydrochloric acid 1 per cent, filtering into a separator. Ammonia is added in excess, and the liquid shaken out with 3 portions of anhydrous ether, the solvent evaporated, and the residue weighed after drying at 100° C.

The authors claim there is no loss on drying at 100° C. but, after driving off the ether the safer procedure would be to bring to a constant weight in a desiccator.

MUSTARD SEED

The German Pharmacopœia contains a method for determining the allylisothiocyanate in mustard seed. The powdered seed is digested with water for two hours; alcohol and a little olive oil added, the mixture distilled and the distillate received in a flask containing ammonia. A known quantity of standard silver nitrate is then added and the mixture digested for an hour on the water-bath. An aliquot is filtered and the excess of silver determined by titrating with potassium thiocyanate.

Each mil N/10 silver nitrate = .004956 gram allylisothiocyanate.

Viehoever has proposed an improved method for determining the allylisothiocyanate. Five grams of the seed in No. 20 powder are placed in a 200-mil flask, 100 mils of water added, stoppered tightly and macerated at 37° C. for two hours.

Then add 20 mils of alcohol (95 per cent) and distill about 50 mils into a 100-mil volumetric flask containing 10 mils of alcohol (95 per cent) and 10 mils of ammonia water (10 per cent). (The mouth of the condenser should extend below the surface of the liquid in the receiver.) Add 20 mils of N/10 silver nitrate to the distillate, set aside twenty-four hours, heat to boiling, cool, fill up to the mark, and filter. To 50 mils of the clear filtrate add an excess of nitric acid (sp. gr. about 1.4) and 1 mil of ferric ammonium sulphate solution (10 per cent), and titrate with N/10 ammonium thiocyanate solution.

State the results in the number of mils of N/10 silver nitrate consumed or in terms of allylisothiocyanate (each mil of N/10 silver nitrate consumed equals 0.004956 gram of allylisothiocyanate.)

NUX VOMICA

The method of the U. S. P. ninth revision is identical with that given for Belladonna, with the exception that the drug in No. 40 powder is used, 10 mils ammonia added, and after shaking, the flask stands ten hours

and is then treated with 25 mils distilled water, 10 mils of N/10 sulphuric acid is used in place of N/50 acid. Each mil of N/10 sulphuric acid corresponds to 36.4 milligrams total alkaloids.

The standard for Nux Vomica in the eighth revision was based on the content of strychnin and not on the total alkaloids, and the separation was effected by means of nitric acid.

The situation with respect to the assay of Nux Vomica is analogous to that obtaining in the case of aconite. The amount of total alkaloids is not necessarily a measure of the therapeutic activity of the drug. Dixon and Harvey[1] report that the relative toxicity of brucin to strychnin has been found to be as 4 : 33, and that the action is quite distinct from that of strychnin, more nearly approaching that of methyl strychnin.

In view of this difference and since the proportions of the two alkaloids are by no means constant, all Nux Vomica preparations should be assayed for their strychnin content. In the eighth revision the alkaloidal residue was dissolved in dilute sulphuric acid, treated with nitric acid, and after standing the strychnin liberated with sodium hydroxide and shaken out with chloroform. This method has been criticised, but the author has found it very satisfactory and has used it to advantage in determining the strychnin content of Nux Vomica. The details are as follows: dissolve the alkaloidal residue in 15 mils 3 per cent sulphuric acid, warming on the water-bath. When cool add 3 mils of a cooled mixture of equal volumes nitric acid 1.42 sp. gr. and distilled water, and after rotating the liquid a few times set it aside for exactly ten minutes, shaking it gently three times during the interval. Transfer the resulting red liquid to a separator containing 25 mils of an aqueous solution of sodium hydroxide 1–10 and wash the flask three times with a very small amount of distilled water, and add the washings to the separator, if the liquid is not turbid add 2 mils more sodium hydroxide. Now add 20 mils of chloroform and shake it well by a rotating motion for a few minutes, allow the liquids to separate, and draw off the chloroform through a small filter wetted with chloroform into a flask; repeat twice, using 10 mils chloroform each time and draw off both portions into the flask using the same filter. Finally wash the filter and funnel with 5 mils chloroform and evaporate filtrate, weighing or titrating the residue as strychnin.

Webster and Pursel[2] found that more definite and complete elimination of the brucin is obtained by treating with nitric acid containing a little sodium nitrite in the presence of sulphuric acid. The separated alkaloids are dissolved in 15 mils of 3 per cent sulphuric acid, to this solution are added 3 mils of a mixture of equal volumes of concentrated nitric acid and distilled water followed by 1 mil of a 5 per cent solution of sodium nitrite. After mixing, the liquid is allowed to stand for exactly thirty

[1] Pharm. J., 1908, 81, 367. [2] Amer. Drug., 1906, 50, 362–3.

minutes with occasional shaking. It is then made alkaline and the strychnin shaken out with chloroform.

The ferrocyanide method of separating strychnin and brucin also gives satisfaction in the hands of careful workers; to make this separation the mixed alkaloids obtained by the U. S. P. assay are dissolved in 15 mils of dilute sulphuric acid and diluted with 100 mils water; 25 mils of 5 per cent potassium ferrocyanide are then added, and the mixture well shaken and allowed to stand six hours. The precipitate is transferred to a small filter, washed with water containing about $\frac{1}{40}$ its volume of dilute sulphuric acid, rinsed into a separator, treated with 5 mils ammonia and shaken out with chloroform. The solvent is run through cotton wool and evaporated and the residue weighed as strychnin.

Matthes and Rammstedt[1] have evolved a method of assay depending on the precipitate formed with picrolonic acid. Fifteen grams of the powdered drug dried at 100° C. are treated with 100 grams ether and 50 grams chloroform, and after a thorough shaking, 10 mils of dilute sodium hydroxide added and the mixture agitated for ten minutes. Fifteen mils of water, or a sufficient quantity to cause the drug to aggregate when shaken, are added and the whole set aside until the solvent separates as a clear liquid; after thirty minutes 50 grams of the solution, representing 5 grams of the drug, are filtered off, evaporated to one-half and 5 mils of N/10 picrolonic acid (dinitrophenylmethylpyrazolone) added to the warm liquid which is then set aside in a cool place for twenty-four hours. The precipitated strychnin-brucin picrolonate is collected in a tared Gooch, washed with 2 mils of ether-alcohol (3–1), dried for thirty minutes at 110° and weighed. The mean molecular weight of strychnin-brucin being 364.32 and that of the picrolonate 628.32, the weight of the latter obtained multiplied by 0.5798 gives the equivalent of mixed bases.

OPIUM

The assay of opium has been the subject of much study and probably more methods have been proposed than for any other drug. The valuation has always been based on its morphin content and the problem has been to separate this alkaloid from some twenty or more others. Nearly all the methods have depended upon the precipitation of morphin, which is then either weighed or titrated. Recently its separation by chloroform-alcohol mixture has been employed with considerable success.

Taylor has given an exhaustive and comprehensive review of the methods of opium assay in the new edition of Allen.

U. S. P., Ninth Revision.—Introduce 8 grams of Opium, which if fresh should be in very small pieces, and if dry in fine powder, into Erlenmeyer flask having a capacity of about 250 mils, add 80 mils of distilled water,

[1] Arch. Pharm., 1907, 245, 112–32.

stopper the flask, and agitate it every ten minutes (or continuously in a mechanical shaker) during three hours. Then pour the contents as evenly as possible upon a wetted filter having a diameter of not over 12 cm., and, when the liquid has drained off, wash the residue with distilled water carefully dropped upon the edges of the filter and its contents, until 120 mils of filtrate have been obtained. Carefully transfer the moist Opium to a mortar by means of a spatula, and rub to a smooth paste, then rinse into the original flask with 50 mils of distilled water, agitate it thoroughly and return the whole to the filter. When the liquid has drained off, wash the residue with 75 mils of distilled water. Evaporate the mixed filtrates and washings on a water-bath to about 40 grams. Transfer the extract to a 50-mil graduated flask and wash the evaporating dish with sufficient distilled water to make the entire volume measure exactly 50 mils when cooled to room temperature. Place in a small mortar 4 grams of freshly slaked lime, add about 10 mils of the opium extract and rub to a smooth paste, then add the remainder of the extract and rinse the flask with exactly 10 mils of distilled water, adding the rinsings to the mortar, and stir frequently during fifteen minutes, avoiding unnecessary loss by evaporation. Filter through a dry filter, about 10 cm. in diameter, and transfer exactly 30 mils of the filtrate, representing 4 grams of Opium, to an Erlenmeyer flask of suitable capacity. To this add 2 mils of alcohol and 15 mils of ether, and, after shaking the mixture, add 1 gram of ammonium chloride, stopper the flask and shake it frequently during half an hour, then set it aside in a cool place for twelve hours or overnight. Remove the stopper and brush any adhering crystals back into the flask. Decant the ethereal layer into a small funnel, the neck of which has been previously closed with a pledget of purified cotton. Rinse the flask and contents with 15 mils of ether, and, when the ether has passed through, wash the funnel and cotton with a small quantity of ether, and then pour the aqueous liquid into the funnel without trying to remove the crystals. Wash the crystals in the flask and the contents of the funnel with distilled water, previously saturated with morphin, until the washings are colorless. Then add a few drops of distilled water to replace the morphinated water. Incline the edge of the funnel over the mouth of the flask and by means of a glass rod carefully transfer the cotton with adhering crystals to the flask. Insert the funnel into the neck of the flask and wash the funnel with 20 mils of N/10 sulphuric acid V. S., followed by 10 mils of distilled water, applied drop by drop around the edge of the funnel. Remove the funnel, replace the cork, warm gently, and agitate until the crystals are dissolved. Rinse the cork with distilled water and titrate the excess of acid with N/50 potassium hydroxide V. S., cochineal T. S. being used as indicator. Each mil of N/10 sulphuric acid V. S. consumed corresponds to 0.028516 gram of anhydrous morphin.

U. S. P., Eighth Revision.—Introduce 10 grams Opium (which, if fresh, should be in very small pieces, and if dry, in very fine powder) into an Erlenmeyer flask having a capacity of about 300 mils, add 100 mils of distilled water, stopper the flask, and agitate it every ten minutes (or continuously in a mechanical shaker) during three hours. Then pour the contents as evenly as possible upon a wetted filter having a diameter of 12 cm., and, when the liquid has drained off, wash the residue with distilled water, carefully dropped upon the edges of the filter and its contents, until 150 mils of filtrate have been obtained. Then carefully transfer the moist Opium back to the flask by means of a spatula, add 50 mils of distilled water, agitate it thoroughly and repeatedly during fifteen minutes, and return the whole to the filter. When the liquid has drained off, wash the residue, as before, until the second filtrate measures 150 mils, and finally collect about 20 mils more of a third filtrate. Evaporate carefully in a tared dish, first, the second filtrate to a small volume, then add the first filtrate, rinsing the vessels with the third filtrate, and continue the evaporation until the residue weighs 14 grams. Rotate the concentrated solution about in the dish until the rings of extract are redissolved, pour the liquid into a tared Erlenmeyer flask having a capacity of about 100 mils, and rinse the dish with a few drops of water at a time until the entire solution, after the rinsings have been added to the flask, weighs 20 grams. Then add 10 grams (or 12.2 mils) of alcohol, shake the flask well, add 25 mils of ether, and repeat the shaking. Now add 3.5 mils of ammonia water from a graduated pipette or burette, stopper the flask with a sound cork, shake it thoroughly during ten minutes, and then set it aside, in a moderately cool place, for at least sixteen hours.

Remove the stopper carefully, and should any crystals adhere to it, brush them into the flask. Place in a small funnel two rapidly acting filters, of a diameter of 7 cm., plainly folded, one within the other (the triple fold of the inner filter being laid against the single side of the outer filter), wet them well with ether, and decant the ethereal solution as completely as possible upon the inner filter. Add 10 mils of ether to the contents of the flask, rotate it, and again decant the ethereal layer upon the inner filter. Repeat this operation with another portion of 10 mils of ether. Then pour the liquid in the flask into the filter, in portions, in such a way as to transfer the greater portion of the crystals to the filter, and when the liquid has passed through, transfer the remaining crystals to the filter by washing the flask with several portions of water, using not more than 15 mils in all. Use a feather or rubber-tipped glass rod to remove the crystals that adhere to the flask. Allow the double filter to drain, then apply water to the crystals, drop by drop, until they are practically free from mother-liquor, and afterwards wash them, drop by drop, from a pipette, with alcohol previously saturated with powdered

morphin. When this has passed through, displace the remaining alcohol by ether, using about 10 mils or more, if necessary. Allow the filter to dry in a moderately warm place, at a temperature not exceeding 60° C. (140° F.) until its weight remains constant, then carefully transfer the crystals to a tared watch-glass and weigh them.

Place the crystals (which are not quite pure) in an Erlenmeyer flask, add lime water (10 mils for each 0.1 gram of morphin) and shake the flask at intervals during half an hour. Pass the liquid through two counterpoised rapidly acting plainly folded filters, one within the other (the triple fold of the inner filter being laid against the single fold of the outer filter), rinse the flask with more limewater and pass the washings through the filter until the filtrate, after acidulating, no longer yields a precipitate with mercuric potassium iodine T. S. Press the filters until nearly dry between bibulous paper and dry them to a constant weight, then weigh the contents, using the outer filter as a counterpoise. Deduct the weight of the insoluble matter on the filter from the weight of the impure morphin previously found. The difference, multiplied by 10, represents the percentage of crystallized morphin contained in the Opium.

Stevens' Method.—Take 8 grams of dried and finely powdered opium and triturate in a mortar with 4 grams of fresh oxide of lime (not air slaked) and 20 mils of water until a uniform mixture results. Add 38 mils of water and stir frequently for half an hour. Filter through a dry 10-cm. filter and transfer exactly 30 mils to a 120-mil flask. To this add 8 mils of alcohol and 20 mils of ether and shake the mixture. Add 1.0 gram ammonium chloride, shake well and frequently for half an hour and set aside in a cool place for twelve hours.

Remove the stopper carefully and preserve, with any adhering crystals, for future use. Pour the ethereal layer into a small funnel, the neck of which has been previously closed with a piece of absorbent cotton. Rinse the bottle with 20 mils of ether, and when this has passed through, pour the contents of the bottle into the funnel. Without trying to remove all the crystals from the bottle, wash the bottle and contents of the funnel with morphinated water until the washings are colorless. When the crystals have drained, place the funnel in the bottle containing adhering crystals, and with a small glass rod drawn out to a curved point, lift the cotton and rinse the crystals into the bottle with 25 mils of N/10 sulphuric acid, using the cotton on the end of the rod to detach any adhering crystals. Place the cotton in the bottle, replace the cork and agitate until the crystals are all dissolved. Rinse the cork and funnel with water and titrate the excess of acid with N/10 potassium hydroxide.

The number of mils of N/10 acid consumed by the morphin, multiplied by 1.516, will give the percentage of crystallized morphin obtained. To this add 1.12 for the morphin remaining in the solution.

Eaton's Method.—Place 1 gram of the dried and powdered sample in a suitable flask, add 100 mils of limewater (U. S. P.) from a pipette, stopper, and shake thoroughly every ten minutes, or continuously on the mechanical shaker, during two hours. Allow to settle, filter rapidly through a dry fluted filter. Remove 50 mils of the clear filtrate and transfer to a separatory funnel (No. 1). Shake out seven times with washed chloroform (chloroform washed with water), using 30 mils each time; collect the chloroform in a separatory funnel (No. 2). Shake out once more with chloroform, transfer this chloroform into another separatory funnel (No. 3), containing 15 mils of clear limewater. Shake up funnel No. 3, withdraw the chloroform, filter, if necessary, and evaporate to dryness. Moisten the residue with a few drops of dilute acid, then add 1 drop of Mayer's reagent. If there is a precipitate, repeat this process of shaking out the original solution with chloroform, washing the chloroform with limewater in funnel No. 3, evaporating, and testing as indicated above, until Mayer's reagent gives a negative test. Now add the limewater in funnel No. 3 to the chloroform in funnel No. 2, shake thoroughly, reject the chloroform, wash the limewater with 30 mils of chloroform, again reject the chloroform and add the limewater to the original solution in funnel No. 1. Add $1\frac{1}{2}$ to 2 mils of a 10 per cent solution of ammonium chloride; or else, neutralize closely with acid, then add ammonia by drops, using no more than 3 or 4 drops in excess. Shake out seven times with a mixture of chloroform and alcohol (2 parts of chloroform to 1 part of alcohol by volume), using 30 mils each time and collecting the chloroform-alcohol in a separatory funnel. Shake out once more with chloroform-alcohol, take about 5 mils of the last shake-out, evaporate to dryness, moisten with a few drops of dilute acid and test with Mayer's reagent. If there is a precipitate, repeat extraction and subsequent testing on a portion until Mayer's reagent gives a negative test. Combine the chloroform-alcohol shake-outs, wash once or twice with 10 mils of water, then in turn wash the water twice with an equal volume of chloroform-alcohol. Filter and wash. Evaporate the chloroform-alcohol to dryness (on the steam-bath), dissolve the residue in 10 mils of warm neutral alcohol, add a convenient excess of N/50 sulphuric acid, evaporate most of the alcohol, and titrate back with N/50 potassium or sodium hydroxid, using cochineal (U. S. P. 5 drops) or methyl red ($\frac{2}{10}$ per cent in alcoholic solution 3 drops), as indicator. If methyl red is used the alcohol need not be evaporated; instead, dilute with about 10 or 15 mils of water before titrating back with alkali. Subtract the number of mils of alkali from the number of mils of acid used. One mil of acid corresponds to 6 milligrams of morphin.

Debourdeaux[1] has shown that there is a variable portion of the morphin in opium which cannot be extracted by water alone. He com-

[1] J. Pharm. Chim., 1911, 4, 13–18, 65–69, 105–112.

pared the methods of the German, Belgian, Swiss, United States, English, and French pharmacopœias and from the results of the investigation concluded that the following methods are the best.

Total Morphin.—Fifteen grams of opium passed through a No. 100 sieve, are triturated with 6 grams of slaked lime of the same fineness. The mixture is diluted with water to 171 grams, agitated frequently for two hours and then filtered; 104 mils or 105.5 grams of the filtrate are shaken first with 10 mils of 95 per cent alcohol, and then with 50 mils ether, 2 grams ammonium chloride are added, and after further agitation to dissolve the salt, the whole is left for twenty-four hours for the morphin to crystallize. The ether is decanted off through a tared Gooch crucible, and the residue is treated with a further 10 mils of ether which is then also passed through the Gooch. The remaining solution with the morphin is now poured into the crucible, which is washed with 6 portions of 5 mils of water saturated with morphin and ether. The washing is continued if necessary until the ammonium chloride is completely removed. The crucible, with the morphin is dried at 100° C., washed with 5 portions of 100 mils each of crystallizable benzol, again dried at 100° C. and weighed.

Soluble Morphin.—Eighteen grams of opium passed through a No. 100 sieve are treated with 144 grams of water, and after agitating two hours the mixture is filtered; 127 grams of the filtrate are triturated with 5.3 grams of slaked lime, and water added until the total weight is 162 grams. After one hour, with agitation, the mixture is filtered and 104 mils, or 105.5 grams, of the filtrate are treated as described above.

Hilton's[1] Modification of the U. S. P., Eighth Method for Opium Preparations.—Transfer 100 mils of tincture of opium or other liquid opium preparation to an evaporating dish and evaporate it on a water-bath to about 20 mils, add 40 mils of distilled water, mix thoroughly and set the liquid aside for one hour, occasionally stirring to disintegrate the resinous flakes adhering to the dish. Having set up a 25-mil Gooch crucible and prepared a matrix of asbestos by pouring some of the solution suspended in water in the crucible, after starting the filter pump, wash the matrix with alcohol and ignite the crucible; when cold, connect the crucible, after emptying the filter flask and rinsing the same with distilled water, pour carefully the contents of the dish into the crucible after starting the filter pump, when all of the liquid has passed through, disconnect the flask and reserve the filtrate for the final evaporation. Connect the flask again and wash the mass on the filter until completely exhausted (indicated by almost a colorless filtrate and the absence of bitterness). Evaporate the washings in a tared dish to a small volume, then add the first filtrate, rinsing the vessel with several small portions of distilled water and evaporate the whole to a weight of 14 grams.

[1] Jour. Amer. Pharm. Assn., 1912.

Proceed as directed under Opium, U. S. P. VIII, beginning "rotate the concentrated solution about in the dish until the rings of extract are redissolved," etc. After standing six hours or overnight as directed, proceed as follows:

Having set up the Gooch crucible, prepare the matrix as previously indicated, wash with alcohol and ignite, cool in the desiccator and weigh, noting the weight of the crucible. Remove the stopper carefully from the flask, and should any crystals adhere to it, brush them into the flask. Wet the matrix in the crucible well with ether, and decant the ethereal solution in the flask as completely as possible upon the matrix in the crucible, after starting the filter pump. Add 10 mils of ether to the flask and proceed as directed in the U. S. P. VIII, using the Gooch crucible for the purpose of collecting and washing the morphine crystals, as therein directed. When this has been completed, remove the Gooch crucible and dry same in the oven at a moderate temperature not exceeding 60° C. (140° F.), until the weight of the crucible and its contents remains constant. Note the weight and deduct the weight of the crucible previously obtained. This gives the weight of the impure Morphin.

Replace the Gooch crucible and pass limewater through the crucible (10 mils for each 0.1 gram of Morphin), reducing the vacuum in the filter flask so that the limewater comes through slowly, dissolving out the morphin, then wash the crucible with more limewater until after acidulation, the washings no longer yield a precipitate with mercuric potassium iodide, disconnect the crucible and dry in the oven ar a temperature of 100° C. (212° F.) to a constant weight, deduct the weight of the crucible; this gives the weight of the insoluble matter in the crucible to be deducted from the weight of the impure morphin previously obtained, this difference represents the percentage of crystallized morphin in 100 mils of the tincture or liquid preparation assayed.

DETERMINATION OF MORPHIN IN TINCTURE OF OPIUM

Evaporate the solution to drive off the alcohol, and if the preparation contains much extracted matter make up to about 25 mils of water and add a slight excess of lead acetate solution. Filter into a 100-mil graduated flask, wash with a little water and to the filtrate add dry sodium phosphate in excess. Make up to the mark with water, filter off 25-mil portions, place in separator and add a slight excess of 10 per cent KOH. Shake out three times with chloroform, collecting chloroformic extracts in the second separator. Wash the chloroform with distilled water, discard chloroform, and run wash water into alkaline liquid. Then shake out four times with 15-mil portions of a mixture of chloroform and alcohol 2 to 1. Separate and evaporate the solvent. The residue will contain any morphin originally present. Dissolve this residue in dilute sulphuric

acid, pour into separator, shake out with 15 mils chloroform. Collect chloroform in a second separator, wash once with water, discard chloroform, run wash water into acid liquid, add a slight excess dilute KOH and extract with chloroform and then with chloroform-alcohol mixture exactly as in the first instance. Finally run the solvent through absorbent cotton loosely stuck into the stem of the separator into an evaporating dish or beaker. The residue may then be titrated for morphin by dissolving in N/10 or N/50 H_2SO_4 and titrating back with N/50 NaOH.

PHYSOSTIGMA

U. S. P., Ninth Revision Method.—Introduce 15 grams of Physostigma in No. 60 powder, into a flask of about 250 mils capacity, and add 150 mils of ether. Stopper the flask, shake it well and allow it to stand ten minutes, then add 10 mils of an aqueous solution of sodium bicarbonate (1 in 20) and shake the mixture vigorously at intervals during four hours. Now add 15 mils of distilled water, again shake the flask well, and, when the drug has settled, decant 100 mils of the ether solution, representing 10 grams of Physostigma. Filter the solution through a pledget of purified cotton into a beaker and rinse the graduate and cotton with ether. Add 20 mils of N/10 sulphuric acid V. S. and evaporate off the ether, stirring during the evaporation with a rubber-tipped glass rod. After the resinous and fatty matter has agglutinated, pour off the acid solution through a wetted filter into a separator. Redissolve the residue in the beaker in about 15 mils of ether, add 2 mils of N/10 sulphuric acid V. S., evaporate off the the ether with continued stirring as before and pour the acid solution on the filter. Repeat this operation until all of the alkaloid is extracted and then wash the filter with distilled water until it is free from alkaloids. Collect the solutions and washings in a separator, add sufficient sodium bicarbonate to make the solution decidedly alkaline to litmus and completely extract the alkaloids by shaking it out repeatedly with ether. Wash the combined ether solutions with 10 mils of distilled water, separate the water completely, and filter the ether solutions, washing the container and filter with ether. Evaporate the ether solution to dryness, dissolve the alkaloids from the residue in exactly 5 mils of N/10 sulphuric acid V. S. and titrate the excess of acid with N/50 potassium hydroxide V. S., using cochineal T. S. as indicator.

Each mil of N/10 sulphuric acid V. S. consumed corresponds to 27.52 milligrams of the alkaloids of Physostigma.

PILOCARPUS

U. S. P., Ninth Revision Method.—Introduce 15 grams of Pilocarpus in No. 60 powder into a 250-mil flask, add 150 mils of chloroform and

proceed as directed under "Belladonna," third line of the assay, beginning with the word "Stopper," and decreasing the amount of water to be added after maceration to 5 mils. The 100 mils of chloroform solution must be drawn off from the bottom of the flask, and dissolve the alkaloids from the residue in 8 mils of N/10 sulphuric acid V. S.

Each mil of N/10 sulphuric acid V. S. corresponds to 20.8 milligrams of the alkaloids of Pilocarpus.

A simple method consists in shaking 20 grams of the powdered drug, or 20 mils of the fluid extract, evaporated on sawdust, with 150 mils of Prolius mixture (ether 4, chloroform 1, alcohol 1) and 4 mils ammonia water; filtering off 75 mils of the clear liquid into a separator and exhausting with 5 per cent nitric acid. The acid solution is then shaken once with chloroform which is discarded, and then made alkaline with ammonia and shaken out with chloroform, the solvent being filtered through a pledget of cotton into a tared dish, evaporated, dried and weighed.

Matthes and Rammstedt[1] have applied their picrolonic acid method to Pilocarpus: fifteen grams of the moderately finely powdered drug are macerated for thirty minutes with 150 grams chloroform and 10 grams ammonia water; 100 grams of the solvent (representing 10 grams of drug) are then filtered off and evaporated to 20 mils; 3 mils N/10 picrolonic acid and 60 mils ether are added, the mixture set aside for twenty-four hours and the precipitate collected on a tared Gooch crucible, washed with 2 mils ether-alcohol 3–1, dried and weighed. The molecular weight of pilocarpin picrolonate is 472.

POMEGRANATE BARK

Method of the German Pharmacopœia.—To determine total alkaloids, pour 90 grams of ether and 30 grams of chloroform upon 12 grams of rather finely ground pomegranate bark, dried at 100° C. and placed in an Erlenmeyer flask. Shake vigorously and add 10 mils of a mixture of 2 parts of sodium hydroxide solution and 1 part of water. Let the mixture stand three hours, shake vigorously at frequent intervals. Then add 10 mils of water, which will cause the powder to gather into balls after vigorous shaking, and leave the supernatant ether-chloroform solution perfectly clear. After an hour, pass 100 grams of the clear ether-chloroform solution through a dry filter, kept well covered and receive the filtrate in a separating funnel. Extract this filtrate with 50 mils of N/10 hydrochloric acid and pass this acid solution, when perfectly clear, through a small filter moistened with water into a 100-mil flask. Make three more extractions with 10-mil portions of water, and pass these extractions through the same filter. Wash the filter with water and dilute the total

[1] Arch. Pharm., 1907, 245, 112–32.

solution with water to 100 mils. Place 50 mils of this solution in a 200-mil flask with 50 mils of water and enough ether to make a layer about 1 cm. thick. Add 5 drops of iodeosine solution and titrate with N/10 potassium hydroxide solution, shaking vigorously after each addition, to give a pale red color to the lower aqueous solution.

1 mil N/100 HCl = .00147 gram mixed alkaloids.

RHUBARB

Tschirch and Edner[1] recommend the use of diazotized paranitranilin for determining the value of rhubarb. The reagent is thus prepared: Five grams of paranitranilin are treated with 25 mils of water and 6 mils of strong sulphuric acid; after agitation, another 100 mils of water and a solution of 3 grams of sodium nitrite in 25 mils of water are added; the whole is then made up to 500 mils with water. The reagent should be protected from the light. From 0.5 to 1.0 gram of powdered rhubarb is boiled with successive quantities of dilute alcoholic potassium hydroxide solution until thoroughly extracted. The bulked filtered solutions are then distilled, and the alcohol-free residue diluted with water; the solution is then acidified with hydrochloric acid, and the precipitate formed on standing is collected, washed with acidified water, and dried. The dry filter and precipitate are then extracted with boiling chloroform for several hours in a Soxhlet apparatus; this removes only the hydroxymethylanthraquinones, leaving rheotannic acid insoluble. The chloroform is distilled off, and the residue dissolved by heating with 10 mils of 5 per cent sodium hydroxide solution and diluted with 50 mils of water. Twenty mils of diazotized paranitranilin solution are then added, and hydrochloric acid, drop by drop, with thorough agitation, until the color of the solution is discharged and an acid reaction obtained. After standing for a few hours, the precipitate formed is collected on a tared filter, washed free from acid, dried at 70° C., and weighed. The weight of hydroxymethylanthraquinones obtained is conveniently expressed in terms of chrysophanol (chrysophanic acid), the molecular weight of the chrysophanolazo-compound being 447 and of that body itself 254; the ratio being, therefore, in round numbers, 4.5 : 2.5. The reaction may be expressed by the following equation, taking chrysophanol as the example:

$$C_6H_4(NO_2)N : NCl + C_{15}H_8O_2(OH)_2 + 3NaOH$$
$$= ((C_6H_4(NO_2)N : NC_{15}H_7O_2(ONa)_2)) + NaCl + 3H_2O.$$

[1] Arch. Phar. 1907, 245, 150.

SABADILLA SEED

T. Ryden[1] gives a method for determining the alkaloidal content of this drug. Ten grams of the powdered sample are shaken one half-hour with 100 mils ether, 10 mils 10 per cent ammonia water are added and the mixture shaken for two hours. The ether is filtered through cotton and 50 mils are concentrated to 10–15 mils. The ethereal solution is shaken out first with 15 mils N/1 hydrochloric acid and then with successive portions of 10 mils water until a drop of the acid solution gives no reaction with Mayer's reagent. The whole of the acid solution is made alkaline with sodium carbonate solution 33 per cent and extracted with 25, 10, and 10 mils of ether, repeating until a drop of the ethereal extract on evaporation gives no reaction with Mayer's reagent. The ethereal extract is evaporated, dried, and weighed or titrated with N/10 acid, 1 mil of which is equivalent to 0.05984 gram of alkaloid.

SANGUINARIA

Fluid Extract.—The assay of the fluid extract is most readily accomplished in the following manner:

Take 10 mils of fluid extract of Sanguinaria, run into acidulated (acetic acid) water; and make up to 250 mils. Filter, and take duplicate portions of 100 mils each, equal to 4 mils of fluid extract. Place the clear red filtrate in a separatory funnel, make alkaline with ammonia, and shake out with chloroform, using 15, 10, 10, and 5 mils successively. A purple coloring matter is removed along with the alkaloid, but it does not interfere with the assay, as is the case with the methods heretofore in vogue. Run the chloroform into a small dish or beaker, and evaporate with gentle heat, or allow to evaporate spontaneously.

The residue of alkaloids and coloring matter is of a resinous consistency, and is not readily soluble in diluted acetic acid, so that solution is best effected by adding 1 or 2 mils of chloroform to dissolve, then running in 20 to 30 mils of N/50 sulphuric acid, and warming on the water-bath until the chloroform is all expelled. The solution of the alkaloid is now washed into a measuring flask and cooled. Mayer's reagent is added to complete precipitation, and the whole is made up to definite volume (50 or 100 mils) with water. This is then filtered, and the excess of acid titrated with N/50 KOH, using phenolphthalein as an indicator.

Since the average of the molecular weights is very close to the molecular weight of chelerythrine, we are justified in assuming that we are estimating pure chelerythrine.

Now calculate the quantity of acid removed with the alkaloid, and

[1] Apoth. Zeit., 1912, 27–104.

from that determine the quantity of alkaloid present. One mil of N/50 acid is equal to .006943 gram Chelerythrin.

Solid Extract.—In the case of an extract made with alcohol, a weighed portion is placed in a flask with about 10 parts of 70 per cent alcohol, acidulated (acetic acid), and warmed until it is dissolved, after which the procedure is exactly as above.

If the extract is an aqueous one, it can be dissolved at once in acidulated water, made alkaline with ammonia, and shaken out with chloroform as above.

Under conditions not yet well understood, heat destroys the alkaloids more or less completely, and it is therefore necessary to avoid the use of heat so far as possible in all manipulations of the drug.

Crude Drug.—For the assay of the crude drug, 5 grams of the powder are moistened with ammonia water, carefully dried, and extracted with chloroform in a Soxhlet apparatus. The chloroform is then expelled from the percolate and the residue treated exactly as in the case of the fluid and solid extracts.

A simple method of assay of Sanguinaria consists in shaking 5 grams of the powdered drug with 150 mils ether and 4 mils ammonia water, filtering 75 mils of the clear liquid into a separator and extracting with 10 per cent acetic acid. The acid solution is filtered into another separator, washed once with petroleum ether which is discarded, and then made alkaline with ammonia, and the alkaloid removed with ether-petroleum ether 2–1. The solvent is filtered into a tared dish, washing filter carefully, evaporated, dried at 100° C. and weighed.

Schlotterbeck's method modified for the fluid extract is as follows: Five mils of the extract are treated with 10 mils of water, and 4 mils of ammonia, and shaken out with two successive portions of 15 mils ether; the aqueous layer is then treated with 10 mils alcohol and exhausted with ether; the combined ether solutions are then evaporated and the residue dissolved in 2 mils chlorofrom. Ten mils of water and 5 mils of N/20 sulphuric acid are added and the chloroform evaporated, the acid solution is stirred and filtered, and the gummy residue extracted twice with acid water, using 3 and 2 mils of the N/10 acid. The alkaloid is then precipitated with excess of Mayer's reagent, the mixture shaken and made up to 100 mils with water, 50 mils filtered off, decolorized with sodium thiosulphate and the excess of acid titrated with N/50 potassium hydroxide.

The factor is .035.

SANTONICA

Several methods have been proposed for estimating Santonin, and the experiences of reputable chemists with these methods has been most

interesting. Caspari, working with the methods of Katz and Thaeter, was unable to get concordant results, or, in fact, any information about the drug which he considered reliable; he prefers Fromme's method, which he claims yielded accurate and reliable data. Nelson found the Katz method satisfactory and, after slight modifications, submitted it to the Association of Official Agricultural Chemists for trial, and the results were concordant. The author has found the Nelson-Katz method easy to handle and apparently capable of yielding accurate results, and has been unable to confirm Caspari's results with the Fromme method. In view of the uncertain situation all methods will be given.

K. Thaeter[1] gives the following process: For the quantitative determination of santonin, 10 grams of the powdered drug are extracted with ether for twelve hours in a Soxhlet tube; the extract, after the evaporation of the ether, is heated for an hour with 5 grams of caustic lime and about 300 mils of water, then filtered and washed with water. The resulting filtrate is acidified with sulphuric acid, warmed until crystals of santonin are formed, when 100 grams of the official solution of aluminium acetate of the German Pharmacopœia are added. The liquid is then evaporated to dryness, the residue is powdered, mixed with 3 grams of magnesium oxide, again moistened with water, dried, and finally, after drying at 105° C., extracted with anhydrous, acid-free ether for five hours. In this manner the total santonin present is extracted, and may be obtained, on the evaporation of the solvent, in pure condition for weighing.

Katz[2] Method.—Ten grams of the coarsely powdered wormwood seeds are extracted with ether for two hours in a Soxhlet apparatus, and after distilling off the ether, the residue is boiled for twenty minutes with a 5 per cent solution of barium hydrate under an inverted condenser. The solution is then cooled and saturated with carbonic acid, filtered quickly, and the residue washed twice with 20 mils of water. The filtrate is evaporated on the water-bath to about 20 mils, then treated with 10 mils of 12.5 per cent hydrochloric acid, left two minutes more on the water-bath and then cooled. The product is placed in a separating cylinder, and shaken with about 20 mils of chloroform, which dissolves the santonin. The chloroform solution is filtered and evaporated, and the residue is boiled with 50 mils of 15 per cent alcohol for ten minutes under an inverted condenser, the solution is filtered hot into a weighed flask, and allowed to stand for twenty-four hours. The alcohol is poured off from the separated santonin through a weighed filter, which is then dried along with the crystallized santonin, and weighed. A correction of 0.006 gram per 10 mils of filtrate must be made for the solubility of santonin in the alcohol.

The method of Fromme is as follows: Thirteen grams of moderately

[1] Arch. der Pharm., 236 (5) 383. [2] Arch. Pharm., 1899, 237–245

finely powdered wormseed are placed in a separatory funnel containing 130 grams of chloroform. A pledget of cotton should be placed in the separatory above the stopcock before introducing the wormseed. After one hour maceration with occasional shaking, 102.5 grams, equal to 10 grams of drug, of the liquid are drawn off into a 200-mil Erlenmeyer flask. Evaporate the chloroform until the residue weighs 7 to 8 grams. Add 100 grams of 5 per cent barium hydroxide solution and place the flask in hot water. After the chloroform has evaporated sufficiently to enable the resin to rise to the surface, it is heated until all odor of chloroform has disappeared. Filter through a plain filter of 6 cm. diameter, previously wetted, into a 200-mil Erlenmeyer flask; rinse the flask and filter twice with 10 mils of hot water, add 5 grams of 25 per cent hydrochloric acid to the filtrate and heat the whole for several minutes on a boiling-water bath. After the liquid has been cooled somewhat by setting the flask in cold water, pour the liquid into a separatory funnel and rinse the flask with 20 mils of chloroform, which is added to the contents of the separatory. Shake the mixture actively for two minutes and after the chloroform has separated perfectly, filter the same through a double plain filter into a 100-mil Erlenmeyer flask. Wash the acid aqueous liquid twice with 15 mils of chloroform by agitation and draw the chloroform off as before through the filter. Distill the chloroform from the combined filtrate and remove the last traces of chloroform from the residue by a current of warm air. Dissolve the residue in 7.5 grams of absolute alcohol and add 42.5 grams of hot distilled water. Filter the milky liquid at once into a tared 100-mil Erlenmeyer flask and wash the flask and filter twice with 10 grams of a mixture of 3 grams of absolute alcohol and 17 grams of distilled water. Set the filtrate aside for twenty-four hours (not longer) and filter through a plain 6 cm. tared filter, washing the flask and filter twice with 10 grams of the above alcohol-water mixture. Dry the flask and filter at 100° C. to constant weight, place in a desiccator for one-half hour and weigh again. To the weight, of the santonin thus found add 0.04 gram for loss by solution in the dilute alcohol. The total weight of santonin multiplied by 10, gives the percentage content, which should be calculated on the basis of previously dried wormseed.

The Determination of Santonin in Santonica (Levant Wormseed.)—E. K. Nelson.—Extract 10 grams of medium-ground Levant Wormseed in a Soxhlet extraction apparatus for three hours with chloroform. Distill off the chloroform till 7–8 grams remain, add 100 grams 5 per cent solution of barium hydroxide, and heat on the steam-bath till the odor of chloroform has disappeared. Boil for five minutes, cool and pass CO_2 (which has been washed through sodium bicarbonate solution to free it from traces of acid which might be carried over mechanically) till saturated.

An excess of CO_2 was found to do no harm. Filter by suction, best on a small Buchner funnel, and wash twice with 10 mils 25 per cent HCl and warm five minutes. Cool till lukewarm and extract with 20, 15, 15 mils chloroform, passing the solvent through a small filter into a flask. Evaporate to dryness, being careful to see that the last traces of chloroform are removed. Add 7.5 grams of absolute alcohol to the residue, and dissolve (by gentle warming if necessary.) Then add 42.5 grams of water heated to 60–70°, stopper the flask and allow to cool. (Right here it is advisable to see that crystallization starts, which can be done by scratching the side with a *minute* crystal of santonin. Samples put aside in a cool place for twenty-four hours, and which contain santonin in liberal amount have been found in a supersaturated condition where this precaution was not observed.) Place the flask in a temperature of 15–17° for twenty-four hours. (Refrigerator compartment away from the ice.) Filter and wash with two portions of 10 mils 15 per cent (by wt.) alcohol. Dry flask and filter at 100°, dissolve santonin left in flask in chloroform and filter into a tared beaker. Wash santonin out of flask and filter thoroughly with chloroform, evaporate filtrate and dry at 100° till all traces of chloroform are gone. To the weight found add 0.04 gram for the santonin dissolved in the dilute alcohol, and multiply the total by 10 for the per cent santonin.

(The solubility factor was found correct for a temperature of 15–17°. At 30–32°, .054 gram santonin was left in solution.)

STRAMONIUM

The method of the U. S. P., ninth revision, is identical with that given for Belladonna, using 15 grams of drug in No. 60 powder, increasing the amount of water to be added after maceration to 25 mils, and, before titration, treating the final residue twice with 5 mils of ether, evaporating each time.

STROPHANTHUS

J. Haycock[1] first percolates the powdered drug with petroleum ether to remove the oil, then dries and exhausts with 70 per cent alcohol. The alcoholic extract is evaporated to a soft extract at a low temperature, dissolved in 100 mils of water, 2 mils of 25 per cent sulphuric acid added and the liquid shaken three times with 20 mils of ether. The aqueous portion is heated to 75° C. for one hour. When cold the strophanthidin formed by the heating, is shaken out with chloroform, the solvent evaporated, a little alcohol added, dried at 65° C. and weighed. The result divided by 0.365 gives the amount of strophanthin present.

[1] Brit. & Co. Druggist, 1911, 59, 94.

Physiological Assay.—A physiological assay probably furnishes the best measure of the therapeutic value of Strophanthus, and the procedure is the same as that described under " Digitalis."

VERATRUM

The literature on the subject of assaying Veratrum is meager, but a determination of the total alkaloids is not difficult.

Bredemann[1] gives a method for the determination of the total alkaloids in Veratrum album: Twelve grams of the powdered drug are treated with 120 mils ether-chloroform 1–1, and 10 mils sodium hydroxide and shaken frequently for three hours; at the end of that time sufficient water is added to agglomerate the drug and after settling the solvent is decanted, clarified with magnesia and a few drops of water, and 100 mils filtered into a separator. It is then shaken out three times with water, acidulated with acetic acid, the acid solution rendered alkaline and extracted with ether chloroform 1–1, the solvent evaporated and the residue dried at 100° C. and weighed.

ASSAYS OF EXTRACTS

Most of the methods have referred to the whole drug, but they may be made readily applicable to the fluid or solid extract. Five to 20 mils of a fluid extract should be evaporated on clean sawdust and the mixture shaken out with the proper solvent. In the case of a solid extract 1–10 grams are taken for a sample, dissolved in water and alcohol and treated by the proper procedure for the drug in question.

The assays thus far have in all cases referred to a single drug and not to mixtures. When dealing with mixtures, which is usually the case in the examination of medicines, modifications will necessarily be in order and preliminary to this a qualitative analysis must be performed. Emphasis on this point cannot be made too strong. When the qualitative examination has shown the component parts of the preparation in question a line of procedure can then be mapped out looking toward a quantitative separation.

THE LLOYD PROCEDURE OF DRUG ASSAY

Before closing the chapter on drug assays, special reference must be made to the absorption method of assay which recently was brought forward by Dr. John Uri Lloyd. A colloidal form of hydrated aluminum silicate is employed, to which the name Lloyd's reagent has been given. On adding it in proper amount to an acid solution of an alkaloid, the alkaloidal salt is brought down.

[1] Apoth. Zeit., 1906, 21, 41–45, 53–56.

By this method all aqueous solutions of alkaloidal salts, so far as Dr. Lloyd has yet determined, will immediately yield the alkaloid, in the form of a precipitate, for the contact with this colloidal reagent destroys the tendency to remain in suspension, the precipitated compound quickly falling to the bottom of the vessel. It is insoluble in water.

From this precipitate, the free alkaloid can be immediately separated by the addition of an alkali, and by extraction with an appropriate solvent, for in the presence of an alkali, the alkaloidal attraction of the reagent is instantly destroyed.

This destroying of the qualities of the reagent, is, however, but a " paralysis " in the presence of the alkali, for after the alkaloid is separated from it, the washing of the residue with a dilute acid brings back to it all its original qualities.

Each alkaloidal salt has an individuality in its affinity for the reagent, the amount necessary for the precipitation ranging from 6 grams of the reagent with 1 gram Codein Sulphate, to 10 grams of the reagent with Quinin Bisulphate in neutral solution, while in acidulated solution, 1 gram of Quinin Bisulphate requires 12 grams of the reagent.

The following table will be of interest:

1 gram	Cocain Hydrochlorate	requires	14	grams of the reagent	
1 "	Strychnin Sulphate	"	10	"	"
1 "	Morphin Sulphate	"	6	"	"
1 "	Brucin Sulphate	"	8	"	"
1 "	Codein Sulphate	"	6	"	"
1 "	Cinchonin Sulphate	"	10	"	"
1 "	Cinchonidin Sulphate	"	11	"	"
1 "	Atropin Sulphate	"	8	"	"
1 "	Quinin Bisulphate (neutral)	"	10	"	"
1 "	" " (acid)	"	12	"	"

The assay of crude drugs by Lloyd's procedure follows the directions given under Hydrastis, page 46.

Dr. Lloyd states that practically all crude alkaloidal drugs can be assayed providing the proper solvents be employed.

Part II

ALKALOIDAL DRUGS, ALKALOIDS AND MEDICINALLY ALLIED SUBSTANCES

CHAPTER III

DEFINITION AND GENERAL METHODS OF SEPARATION AND IDENTIFICATION

The term alkaloid is, in general, limited to those organic bases which are found in the organism of the plant. But as it is necessary to include under the classification of alkaloids those artificial basic substances which of late have become very important in medicine, and which both in composition and reactions are closely related to the natural bases, the limitation of origin requires an exception.

The alkaloids do not form a well-defined group in a rational classification of organic compounds. They are usually complex substances. They all contain nitrogen, but rarely more than two atoms to the molecule, exceptions being in the Xanthin group and some of the rarer bodies, though there may be from twenty to forty carbon atoms. The basic property of the greater number is shown by the ease with which they form well-defined salts with acids, and the fact that they are not removed from acid solutions by immiscible solvents; but this is not invariable, and with some bodies the salts are unstable, being decomposed by water alone, and the alkaloid will have distinctly acid properties and will be removed from an acid aqueous solution by immiscible solvents.

The greater number have been found to be derivatives of pyridin and quinolin, while there are many that cannot be correlated with these bases. Caffein and theobromin possess a constitution which is in no way related to pyridin, being derivatives of uric acid.

Betain and muscarin, together with cholin and also sinapin, form a special group of quaternary bases, closely related to the amines of the aliphatic series. The weak bases, leucin and glutamin, which are decom-

position products of albuminoid matter, and which have been found in numerous plants, belong to the amido acids of the aliphatic series, the asparagines.

They are nearly all solids, though coniin, nicotin, spartein, pelletierin, trimethylamin, and some other lesser known alkaloids, are liquids, and others, as physostigmin, scopolamin, usually appear in the liquid state, being very hygroscopic. Most of them are sparingly soluble in water, but usually soluble in alcohol and chloroform, benzol and ether, and their solutions are generally alkalin and bitter. The salts are formed by the direct union of a base with an acid, without the separation of water, and as a rule the salts are soluble in water.

The hydrochlorides resemble those of all amines, as well as the chlorides of the alkali metals and the ammonium bases, in forming crystalline double salts with platinic chloride, mercuric chlorid, and auric chloride. Most of the alkaloids may be precipitated from their acid solutions by potassio-mercuric iodide, potassio-bismuthic iodide, picric acid, tannic acid, phosphotungstic acid, and phosphomolybdic acid, and also by a solution of iodine and potassium iodide, the latter reagent precipitating a large number of alkaloids quantitatively.

Separation and Purification of Alkaloids.—The chemist analyzing drugs and medicinal preparations will be called upon to identify and determine alkaloids in complex formulas at the same time that the other components are sought, and to separate, identify, and determine alkaloids where the object of the analysis is the determination of the alkaloids alone. The scheme of analysis to be pursued in the first instance has been fully elaborated in my work "Qualitative Analysis of Medicinal Preparations." Where the alkaloids alone are the substances sought the following procedure will be found advantageous, the preliminary work depending on the character of the sample. If the material is of an animal nature, i. e., a stomach, intestine, liver, meat, or the like, it should be thoroughly disintegrated in a meat chopper or sausage machine, the cleanliness of which has been previously ascertained, then mashed in a mortar to a pulp and incorporated with a little tartaric acid. The mixture is then transferred to a large beaker or Erlenmeyer flask, water added, the flask warmed on a water-bath and the digestion continued for several hours, stirring from time to time. The liquid is decanted and the mass washed two or three times with warm water, not in too large amounts, as it is desirable to prevent the final volume from becoming too unwieldy; a little alcohol is then added to the decanted liquid and washings, and if a cloudiness appears, more is added until a precipitate separates in flocks, the latter condition often being facilitated by warming. After the precipitate has settled, the liquid is decanted through a creased filter and the container and filter washed with dilute alcohol. The filtrate is then transferred to a large

separator, ammonia added in slight excess, and the liquid shaken out four times with ether. A small amount of the ether from the fourth shake out is evaporated, the residue dissolved in a few mils of dilute sulphuric acid, filtered and tested with Mayer's reagent, and if a precipitate occurs, the shaking out with successive quantities of ether continued. The combined ethereal liquids are then run through a creased filter and evaporated, hastening the evaporation with an air current.

If morphin is suspected, the shaking out with ether is dispensed with and the aqueous alcoholic solution, after filtering, is evaporated until nearly dry and the mass extracted several times with alcohol, filtering the solvent into an evaporating dish. After evaporating the alcohol, the residue is dissolved in dilute sulphuric acid, filtered into a separator, a slight excess of ammonia added and shaken out four or five times with chloroform-alcohol 2–1, the solvent being run off through cotton and evaporated.

The treatment of the crude alkaloidal residue obtained by either of these two methods will be considered later.

If the original sample is a pill, tablet, evaporated extract or other solid substance partly insoluble in water, it should be extracted several times with warm 95 per cent alcohol (pills, tablets and other hard solids must be ground in a mortar) the solvent filtered and evaporated nearly to dryness. The residue is treated with dilute sulphuric acid and filtered into a separator, washing the dish and filter with warm water, the filtrate made alkaline with ammonia and shaken out until exhausted with Prolius mixture (ether 4, chloroform 1, alcohol 1) and if morphin is suspected, several final extractions with chloroform-alcohol 2–1 must be made. The combined solvent solution is then run through absorbent cotton or a creased filter and evaporated to obtain the crude alkaloidal residue.

If the sample is an alcoholic liquid, water is added until gums and resins and other substances are precipitated and the liquid filtered into a separator, or if no alcohol is present the liquid is poured directly into a separator. Ammonia is added in slight excess and the mixture shaken out as described in the preceding paragraph. In the case of aqueous mixtures containing a large quantity of sugar, the final shaking with chloroform-alcohol may produce an emulsion, and under these conditions the solution should be first evaporated until most of the liquid is driven off and the residue extracted several times with hot alcohol. The latter is evaporated, the residue treated with dilute sulphuric acid, filtered into a separator and shaken out with the solvent.

The crude alkaloidal residue obtained by any one of the above procedures is then treated with 10–15 mils of dilute sulphuric acid, warmed and the solution filtered into a small separator. The residue is treated twice more with small quantities of normal sulphuric acid which is run

through the filter into the separator. After the liquid is cooled, it is shaken out four times with 25-mil portions of chloroform, the combined chloroformic extracts washed with 10 mils water, preserving the wash water and adding it to the acid liquid, the chloroform run through absorbent cotton lightly plugged in the stem of the separator and evaporated. The residue left on evaporating the chloroform will contain caffein, theobromin, colchicin, narcotin, hydrastin, geissospermin, piperin, quebrachin, antipyrin, anesthesin, subcutin, or propaesin. After evaporating the chloroform the acid solution in the separator is made slightly ammoniacal and shaken out three times with anhydrous ether, the combined ethereal liquids are washed once with 10 mils water, filtered into a beaker and evaporated. The ammoniacal liquid should then be shaken out with chloroform, the solvent washed, filtered and evaporated, and the ammoniacal liquid finally extracted with chloroform-alcohol 2–1, the solvent filtered and evaporated.

If a separation such as above described is made on an unknown mixture, the alkaloidal residue should be obtained in a tared beaker and weighed as it will often be necessary, especially in forensic work, to know the quantitative proportions. The final evaporation and in fact the dissipation of the last portions of the solvents in all evaporations during the procedure should be done with great caution as many of the alkaloids are volatile, below 100° C. In cases where delicate questions are involved the residue should be dried *in vacuo* over sulphuric acid or calcium chloride.

In order to identify the constituents of the residue the procedure should be systematic and thorough, but if the quantity is especially small, a milligram or less, the tests employed must be carefully chosen and a procedure to be used in such a case will be discussed later.

First let us consider the residue left on evaporating the chloroform used for shaking out the acid solution. A macroscopic examination will usually indicate the presence of caffein or theobromin. The residue is then dissolved in about 5 mils of chloroform and a couple of drops of the solution evaporated on watch glass, and the residue dissolved in 1 mil of dilute sulphuric acid, the acid solution is then treated with a drop of Mayer's reagent and any precipitate noted, which would occur if colchicin, narcotin, hydrastin, quebrachin or antipyrin are present, and of course, if none is obtained further tests for these substances are unnecessary. Then a few drops of the chloroform solution should be evaporated in a small dish, the residue removed on the end of the finger (previously well washed) and rubbed over the end of tongue when the physiological effect of piperin and the synthetic anesthetics will be noted. A murexide test is then to be performed for the purpose of detecting caffein and theobromin on another portion of the evaporated chloroform solution. Then other por-

tions are evaporated and tested respectively with nitric acid, Froehde's reagent, formaldehyde sulphuric acid and any characteristic coloration due to colchicin, narcotin, hydrastin, geissospermin or antipyrin noted. Further tests for substantiating the particular alkaloid indicated will be found under the detailed description of the individual.

The examination of the alkaloidal residue from the alkaline solution when the amount is comparatively large should be as follows: After noting the odor which will be characteristic if nicotin, coniin, spartein are present, the whole amount is dissolved in 10–15 mils of chloroform and a drop of this solution on evaporation tested with Mayer's reagent to determine whether an alkaloid is actually present, and then a small portion is tested physiologically on the tongue for the presence of coca alkaloids, anesthetics, and aconitin. Next a residue in a small evaporating dish is treated with two drops of concentrated sulphuric acid and the color noted; red indicating sanguinarin and lobelin; yellow to red, sabadin, sabadinin, and atisin; blue, geissospermin or quebrachin; then on dilution with a few drops of water and pouring into a small test-tube, a fluoresence will be noted if quinin and some of the cinchona alkaloids are present. The same quantity of residue is then treated with sulphuric acid containing potassium bichromate in solution and freshly made, and any color change carefully noted; strychnin, yohimbin, gelseminin, papaverin, and quebrachin will be indicated by this test. Another residue is then treated with a few drops of concentrated nitric acid and the color carefully noted; brucin, aconin, morphin give a red color, sanguinarin orange, physostigmin, yellow soon turning orange; ipecac alkaloids orange; codein, yellow with the crystals orange until dissolved; heroin, yellow gradually becoming green; veratrin, pink rapidly fading; orthoform, blue changing to red; gelsemin, gelseminin, and geissospermin purple red; after noting the color in the cold the acid is evaporated on the steam-bath, antipyrin will be indicated by the appearance of a purple color and physostigmin gives a blood-red residue turning deep green and gelsemin a blue green. After the last traces of acid are evaporated the dish is cooled and a few drops of alcoholic potash added and the color and odor noted; strychnin, yohimbin, atropin, hyoscyamin, scopolamin and antipyrin give a purple color; holocain, nirvanin, novocain, orthoform and subcutin, red; the odor test is especially characteristic; cocain, aconitin, tropacocain, and stovain giving ethyl benzoate, which in the latter case is accompanied by isonitrile, and on warming this may be accentuated; a disagreeable odor appears in the presence of alypin, holocain, and nirvanin; euphthalmin gives off the odor of benzaldehyde and ethyl cinnamate is noticed if the cinnamyl bases of coca leaves are present.

Another portion of the residue is now treated with a few drops of sulphuric acid containing formaldehyde, which will give purple colorations

of varying degrees of intensity and shades when certain of the opium alkaloids and their allied synthetic derivations are present; these include morphin, codein, heroin, dionin, apomorphin, narcotin, papaverin, apocodein. Aconin gives a blue color and subcutin salmon, but the latter would have come out in the acid shake out.

These tests will indicate a large number of the alkaloids commonly met with except pilocarpin and pelletierin. Microchemical tests should now be resorted to. A portion of the chloroform solution is evaporated and the residue dissolved in a few drops of very dilute hydrochloric acid, drops transferred to separate microscopic slides and tested respectively with reagents which give characteristic microscopic precipitates.

It will often be found useful to test the physiological action of an alkaloidal residue on a cat's eye, and to prepare the solution for making this test, the amount reserved should be dissolved in a small quantity of dilute acetic acid, filtered, and brought to neutrality with sodium bicarbonate. The solution may be applied with a medicine dropper and to one eye only of an individual subject, the animal being strapped to a trough-shaped apparatus specially designed for this sort of work. After the operation the animal ought to be liberated and returned to the cage and observations of the effect of the drug made from time to time. Atropin, homatropin, hyoscyamin, scopolamin, gelseminin, and gelsemin produce dilation; physostigmin and pilocarpin cause contraction, though in case of the latter dilation will occasionally take place.

Returning now to a discussion of the procedure to be observed in the case of very small residues, one must first take into consideration the question involved. If it is a toxicological case the tests must be chosen with care after first obtaining all the information possible regarding the history of the case. No hard-and-fast rule can be laid down until one has familiarized himself with these facts. The residue should be dissolved in 5 mils of chloroform and several drops evaporated on microscopic slides, the residues dissolved in weak acid and precipitated with reagents giving the most characteristic precipitates and their forms observed under the microscope. Cocain, strychnin, codein, heroin, morphin, atropin, hyoscyamin, scopolamin, aconitin, and some of the synthetic anesthetics should be especially sought for in this examination. Then test small fractions of the solution after evaporation as described above with sulphuric acid and bichromate, nitric acid and alcoholic potash, formaldehyde-sulphuric acid, and by the physiological tongue test.

Microchemical Examination of Alkaloids.—The identification of alkaloids by a microscopic examination of the precipitate obtained on adding a reagent to a dilute solution of the specimen has assumed considerable importance during the last few years and has been a marked step in the progress of analytical chemistry. Howard and Stephenson took up the

work in 1908 at the Bureau of Chemistry, beginning a systematic investigation of the action of all possible reagents on all the pure alkaloids obtainable in order to determine and sift out the characteristic forms, to determine the effect of an alkaloid on another and finally to work out a scheme of analysis based on the results obtained. They have made considerable progress in the direction contemplated, but their results have never been published in full.

In making these tests it is desirable to have the alkaloids in a solution diluted from 1–100 to 1–200. The reagents giving the greatest satisfaction include N/10 iodine, 10 per cent platinic chloride, 5 per cent palladous chloride, gold chloride, picric acid, potassium permanganate, potassium chromate, chromic acid. A drop of the solution to be tested is transferred to a microscopic slide, the instrument adjusted and then a drop of the reagent added and the observation made. It will be necessary in some cases to start the crystallization by stirring the liquid with a glass rod. Another procedure consists in transferring a bit of the alkaloidal residue to a slide by means of a needle or glass rod, dissolving it in a drop of dilute hydrochloric acid and then adding the reagent.

Strychnin is one of the easiest substances to detect microscopically. Howard notes thirty-six crystalline precipitates given by this alkaloid. Berberin, tropacocain, and cocain also react well with reagents, and Howard's notes on the reactions given by the latter are detailed under the analytical properties of cocain later in the book.

Putt,[1] working with iodine, platinic chloride, and palladous chloride as reagents, has reproduced a number of plates showing the crystalline precipitates given by morphin, codein, dionin, atropin, β-eucain, cocain, nicotin, antipyrin, strychnin, and heroin.

Grutternik[2] experimented with the ammonium salts of various organic acids as precipitants and reports as especially suitable the following: *m*-nitrobenzoic acid for strychnin; *p*-nitrobenzoic acid for strychnin and tropacocain; dinitrobenzoic acid for hydrastin, novocain, brucin, and strychnin; trinitrobenzoic acid for novocain, tropacocain, strychnin, brucin and coniin; dihydroxybenzoic acid for cinchonin; trihydroxybenzoic acid for quinidin; mellitic acid for quinidin and cinchonidin; naphthalene sulphonic acid for cocain and strychnin; *p*-nitrophenylpropiolic acid for hydrastin, hydrastinin, strychnin, tropacocain, cinchonidin, and nicotin.

Seiter and Enger[3] have recorded the results of their investigations on the precipitates given by cocain and some of the synthetic anesthetics with gold and platinum chlorides, chromic acid, and permanganate. The residue under examination is made up to 20 per cent solution with dilute

[1] Jour. Ind. and Eng. Chem., 1912, 4, 508–12.
[2] Z. anal. Chem., 1912, 51, 175–234.
[3] Am. J. Pharm., 83, 195–201; 265–8.

hydrochloric acid for the permanganate test and diluted to 1 per cent for the others. Cocain is the only common anesthetic giving a precipitate with permanganate; alpha- and beta-eucain and holocain give precipitates with platinic chloride differing from cocain; alpha-eucain and stovain give precipitates with gold chloride differing from cocain; with chromic acid cocain alone forms crystals. Seiter states further that in dilutions of 1–3000 cocain can be detected by treating 1 mil of the solution with 1 drop 25 per cent sulphuric acid and 1 mil saturated permanganate, allowing it to stand for some time and examining a drop of the mixture on a slide for the characteristic violet-red rectangular plates; alphaeucain at 1–600 gives crystals resembling ammonium-magnesium phosphate.

The subject of the micro-analysis of alkaloids and certain other plant principles is featured by Kraemer in his "Botany and Pharmacognosy."

Quantitative Estimation of Alkaloidal Residue.—It is a good rule always to make the evaporation of the final extraction of an alkaloid in a tared beaker and weigh the residue. The worker will then have made his quantitative estimation regardless of the character of the residue and he can then proceed to identify the mixture. If the alkaloid is extracted according to the method which has been detailed on the preceding pages and all the precautions taken to avoid loss by spurting and contamination with the salts dissolved in the aqueous liquids, and the final menstruum filtered through cotton, the weight of the residue will give the best determination of the quantitative value of the preparation under consideration. This statement is especially true when one is working with drugs containing more than one alkaloid, a condition which will obtain in the majority of instances with natural drugs. A residue obtained from coca leaves never consists entirely of pure cocain, from nux vomica of strychnin alone, and any titration or precipitation method must take for its factor either the molecular weight of cocain or strychnin, or the mean of mixtures, the exact proportions of the ingredients of which are never the same. When working with a mixture containing but a single alkaloid, the latter, after a careful extraction, can be titrated with satisfactory results. The writer has often checked volumetrically the figures obtained in a gravimetric estimation of a single alkaloid extracted according to the previous directions and obtained figures which showed that the alkaloid was in a state of practical chemical purity.

For making a volumetric estimation, the residue should be dissolved in 50 mils of N/50 sulphuric acid and titrated back with N/50 potassium hydroxide, using methyl red as an indicator. It will be necessary often to warm the acid to hasten solution and one should be cautious that any ring of alkaloid which often collects near the rim of the beaker is dissolved by the acid. The residue may also be dissolved in a few mils of neutral alcohol and then treated with the acid.

TABLE OF THE FACTORS FOR N/50 ACID

One mil of N/50 Sulphuric Acid V. S. is the equivalent of:

	Gram
Sulphuric acid	0.0009809
Aconitin	0.012907
Atropin	0.0057838
Cinchona, combined alkaloids of	0.0061841
Cinchonidin	0.005884
Cinchonin	0.005884
Cocain	0.0060636
Coniin	0.002543
Hydrastin	0.0076636
Ipecac, combined alkaloids of	0.0048034
Morphin, anhydrous	0.0057032
Morphin, crystallized	0.0060636
Physostigmin	0.005504
Pilocarpin	0.004163
Quinin, anhydrous	0.0062842
Strychnin	0.006684

Heikel[1] has worked out a method of determining alkaloids in solution by adding an excess of Mayer's reagent and titrating the excess of mercury with potassium cyanide and silver nitrate. A solution of the alkaloid is made containing 0.1 gram in 10 mils; Mayer's reagent is then added to 10 mils of the solution until there is about 15 mils in excess; the liquid is diluted to 100 mils, shaken, filtered and 80 mils of the filtrate treated with 10 mils of dilute ammonia and 10 mils N/20 potassium cyanide which precipitates all of the mercury. The mixture is then neutralized or acidified with dilute sulphuric acid and N/20 silver nitrate added until there is a permanent turbidity. From this titration the amount of mercuric chloride actually precipitated by the alkaloid can be determined.

TABLE SHOWING THE WEIGHT OF ALKALOID CORRESPONDING TO 1 MIL N/20 MAYER'S REAGENT

Aconitin	0.0159 gram	
Atropin	0.0093 gram	
Berberin	0.0092 gram	
Brucin	0.0112 gram	
Quinin and Quinidin	0.00895 gram	titration in neutral solution
Quinin and Quinidin	0.00514 gram	
Cinchonin and Cinchonidin	0.0087 gram	titration in neutral solution
Cinchonin and Cinchonidin	0.00514 gram	

[1] Chem. Zeit., 1908, 32, 1149–50, 1162–63, 1186–87, 1212–13.

Cocain	0.0082 gram	
Colchicin	0.00144 gram	
Heroin	0.00122 gram	
Hydrastin	0.00116 gram	
Hyoscyamin	0.0093 gram	
Ipecac alkaloids	0.00895 gram	
Morphin	0.0104 gram	titration in neutral solution
Morphin	0.0811 gram	
Physostigmin	0.0084 gram	
Pilocarpin I	0.00765 gram	amorphous precipitate
Pilocarpin II	0.00369 gram	crystalline precipitate
Spartein	0.00213 gram	
Strychnin	0.00835 gram	
Veratrin	0.0192 gram	

Classification of Alkaloids.—The alkaloids and the drugs in which they occur will be discussed in the following order. The classification is based on that of Pictet, but it has been modified in so far that certain alkaloids of unknown or indefinite composition have been described under the same group as those having a known derivation, the change being advantageous on account of similarities in chemical properties and medical usage. The names in large type signify the bases whose composition has been definitely or with reasonable certainty established, or which have been classified according to derivation.

Alkaloids derived from pyridin.
- CONIUM ALKALOIDS
- PIPERIN
- ARECA ALKALOIDS
- PILOCARPUS ALKALOIDS
- SPARTEIN
- Lobelin
- CYTISIN
- Delphinium alkaloids
- Piturin

Alkaloids derived from pyrrolidin.
- SOLANUM ALKALOIDS
- POMEGRANATE ALKALOIDS
- COCA ALKALOIDS

Alkaloids derived from quinolin.
- CINCHONA ALKALOIDS
- Yohimbe alkaloids
- Quebracho alkaloids
- Pseudocinchona alkaloids
- Angostura alkaloids
- Alstonia alkaloids
- Geissospermum alkaloids

Alkaloids derived from isoquinolin.

OPIUM ALKALOIDS

Ipecac alkaloids

HYDRASTIS ALKALOIDS

Berberis alkaloids

Calumba alkaloids

CORYDALIS ALKALOIDS

Celandine alkaloids

Sanguinaria alkaloids

Alkaloids which probably contain a pyridin nucleus but in a condition of condensation as yet unknown

STRYCHNOS ALKALOIDS

PEGANUM HARMALA ALKALOIDS

ACONITE ALKALOIDS

VERATRUM ALKALOIDS

Alkaloids containing no pyridin nucleus.

COLCHICIN

XANTHIN BASES

ERGOT ALKALOIDS

MUSTARD SEED ALKALOIDS

Alkaloids of unknown composition.

Physostigma alkaloids

Anhalonium alkaloids

Pareira alkaloids

CHAPTER IV

ALKALOIDS DERIVED FROM PYRIDIN

CONIUM ALKALOIDS

Coniin, $C_8H_{17}N$
Methyl-coniin, $C_9H_{19}N$
Gamma-Conicein, $C_8H_{15}N$
Conhydrin, $C_8H_{17}NO$
Pseudo-conhydrin, $C_8H_{17}NO$

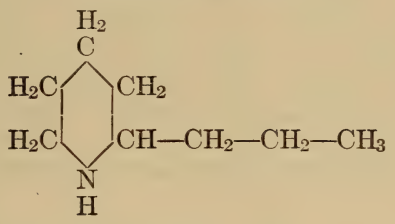
The hemlock, Conium maculatum L (Umbelliferæ), contains these bases in combination with vegetable acids. They are found in all parts of the plant, but particularly in the fruit before it is fully ripe, the fruit being the portion used as the drug. It is seldom adulterated, being used itself more as an adulterant of anise, which it closely resembles in appearance. The alkaloids are all volatile and occur in the fruit to the amount of 0.5 to 1.5 per cent, the average being about 1 per cent. Coniin predominates, in fact the proportions of the other alkaloids are very small, conhydrin, the next in quantity, being present in only about one-twentieth the quantity according to Wertheim. Taylor in the new edition of Allen also records the presence of ethyl-piperidin, but does not give any detailed description of its occurrence or properties, and it is not mentioned by Pictet or Bruhl. It has been claimed that coniin is present in Sambucus nigra.

Conium extract and the alkaloid coniin have but a limited use in medicine. The extract is used in preparations which are used for controlling spasmodic affections like whooping cough, also in chorea and in certain forms of insanity. It is employed in palliatives for cancerous and scrofulous ulcers and tumors, and in certain forms of skin diseases. In plasters it is sometimes combined with belladonna for intercostal neuralgia. In ointments it is used for fissures and hemorrhoids. In fluid extract dandelion compound it occurs combined with Taraxacum and Podophyllum.

In the form of pills or tablets, Conium extract is combined with aloes, ferrous sulphate, and ginger; with ipecac; with cubeb and glycyrrhiza; with mercurous iodid, lactucarium and opium in syphilitic compounds;

and with Hyoscyamus, ignatia, opium, belladonna leaves, stramonium, aconite leaves and Cannabis sativa in a neuralgic idiopathic formula. In the liquid form we find elixirs of Conium with pyrophosphate of iron. The pure alkaloid in the form of the hydrobromate is used in tablet triturates and hypodermatic tablets.

Coiin. d-alphapropylpiperidin



Naturally occurring coniin is dextrorotatory and when pure is a colorless, oily liquid with a tobacco-like odor, which on dilution with water becomes mousey, and is the characteristic odor by which the alkaloid is recognized. Coniin darkens by age or by exposure to light. It melts at $-2.50°$ C., boils at about 166° C., distills readily with steam or with alcohol vapor, and is volatile at the ordinary temperature. It has $(a)_D = +16.4°$ at 19°, but on dilution with solvents the rotatory power is diminished; the specific gravity is 0.8444 at 20° C. Coniin is soluble in water 1–50, the solution having a strongly alkaline reaction, and giving a pink color with phenolphthalein; this coloration is not removed by chloroform, as is the case with nicotin under similar conditions. Coniin is readily soluble in alcohol, ether, petroleum ether, and other organic solvents. With carbon disulphide it forms a definite compound which remains in the form of needle-like crystals on evaporating the solvent.

The hydrochloride of coniin is formed with great readiness. On inverting a beaker moistened with hydrochloric acid over a drop of the alkaloid, white fumes will be produced and the crystalline hydrochloride formed. The phenomenon is similar to that given by nicotin, but in the case of the latter an amorphous hydrochloride results. The hydrochloride may also be produced by passing dry hydrogen chloride through a solution of coniin in anhydrous ether.

The pure alkaloid on exposure to bromine vapor is converted to a mass of white crystals. It is readily oxidized by bromine water, chromic, and nitric acid, butyric acid being given off, and easily recognized by its odor.

It is precipitated by nearly all of the general alkaloidal reagents, but the solutions must not be too dilute. No precipitates are given by gold or platinic chlorides at dilutions of 1–100, while with nicotin precipitates will be obtained with these reagents with dilutions from 1–5000 to 1–10000.

Coniin gives no precipitate with silicotungstic acid at a dilution greater than 1–5000, while nicotin in dilution of 1 part to a million will yield a precipitate.

Gabretti[1] describes a test with sodium nitroprusside which consists in adding a solution of the reagent to a dilute solution of the alkaloid. No color is produced at first, but on stirring a red tint appears, finally turning yellow. The color is destroyed by acids and changed to bright yellow with alkalies. Nicotin does not give this reaction.

This reaction is apparently due to the secondary amine-like character of the coniin molecule. Coniin when subjected to Simon's [2] test for secondary amines, gives an orange-red color. The reaction is obtained by adding one drop to 3 mils of water followed by 1 mil of dilute acetaldehyde in 50 per cent alcohol and 1 drop of 1 per cent sodium nitroprusside.

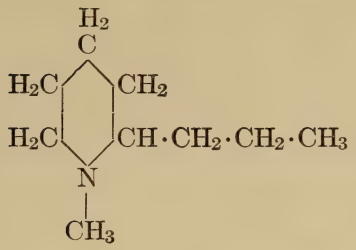
The reaction of coniin with carbon bisulphide has been elaborated by Dilling and applied as a test for coniin and the other alkaloids of hemlock. About 0.5 mil of a strong alcoholic solution of the alkaloid is boiled with a few drops of bisulphide and then an excess of water added. The solution thus obtained is now divided and the portions treated with a few drops of solutions of copper sulphate, ferric chloride, ferric sulphate, nickel chloride, cobalt chloride, and uranium nitrate, which will produce different colors, and on shaking with ether or toluene the shades will usually go into the solvent. Coniin gives a red color with uranium nitrate and toluene which is especially characteristic. Nicotin does not give these reactions, but piperidin reacts in a way almost identical with coniin. The color obtained in the copper sulphate reaction is brown; with ferric chloride, brown; with ferric sulphate, purplish brown; with nickel or cobalt chlorides, green. Spartein and lobelin, two volatile alkaloids, give a greenish yellow or no color with copper.

The crystalline salts of coniin include the hydrochloride melting 218°; hydroiodid melting 165°; hydrobromide melting 211°; picrate, small yellow prisms melting 75°; aurochloride, golden yellow crystals melting 77°; and cadmio-iodide melting 118°; platinic chloride containing 1 molecule H_2O melting 78°; anhydride 175°; picrolonate melting 195.5°.

Coniin may be prepared synthetically by the reduction of allyl-pyridin in alcohol by sodium. The synthetic product is inactive, but when there is added to a very concentrated and rapidly evaporating solution of its bitartrate, a crystal of *d*-coniin bitartrate prepared from the natural coniin, the *d*-coniin salt will entirely crystallize out and the *l*-coniin remain in solution; *l*-coniin platinic chloride melts at 160°, *l*-coniin aurochloride melts at 59°.

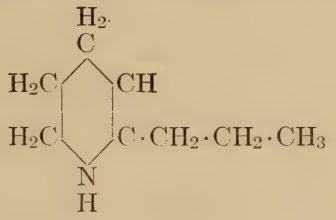
[1] Boll. Chem. Farm., through Pharm. J., 1907, 78, 59.
[2] Compt. rend., 125, 1897, 536.

Methyl-coniin



This alkaloid is a colorless, lævorotatory liquid, boiling 173–174°, with specific gravity .8318 at 24° C.

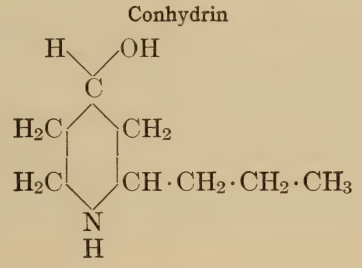
γ-Conicein. α-Propyltetrahydropyridin.



Commercial coniin contains traces of this alkaloid. It is a colorless liquid, with an odor like coniin, boiling 171–172°, specific gravity .8825 at 22.5° C., remaining liquid at −50° C., and optically inactive. It is but slightly soluble in water, the solution having a strong alkaline reaction. The α form may be prepared from coniin by decomposing the bromo-derivative with alkali, and is easily reduced to inactive coniin by tin and hydrochloric acid or sodium and alcohol. It yields a characteristic double salt with stannic chloride, melting 215° C. The auro-chloride melts at 69–70°; picrate 62°; hydrochloride 143°; hydrobromide 139°; and hydro-iodide at 102°.

α and β coniceins are obtained by the action of phosphoric anhydride or fuming hydrochloric acid on conhydrin, the former is a liquid boiling at 158° and the later a volatile solid melting at 41°, boiling at 168°.

Conhydrin



Conhydrin crystallizes from ether in dextrorotatory colorless leaflets, melting at 118–121°, boiling at 220–225°, readily soluble in alcohol, chloroform and moderately soluble in water and ether. It sublimes easily, its odor resembles coniin, and it may be separated from commercial coniin by cooling the liquid to 5° C. collecting the separated crystals on glass wool, and washing with petroleum ether. Its aurochloride melts at 133–134°. Its proportion to coniin in hemlock is about 1–20.

On heating conhydrin with phosphorus pentoxide in a sealed tube in an atmosphere of hydrogen, β-conicein results.

Pseudoconhydrin

This alkaloid is the stereo-isomer of conhydrin and crystallizes in various forms, melting at 100–106°, boiling at 230–236°, dextrorotatory $(\alpha)_D = +10.98°$, soluble in water and organic solvents. Its aurochloride on decomposition gives the normal conhydrin. On crystallizing out of petroleum ether the melting-point is 52–69°, but on warming, this form is converted to that having the higher melting-point, 133–40°. The platinochloride melts at 185–186°.

J. von Braun[1] has evolved a procedure for the separation of the conium bases. The greater part of the coniin is first separated by fractional distillation leaving the conhydrin in the mother liquor. The distillate is then treated with benzoyl chloride and sodium hydroxide, which gives benzoyl coniin and benzoyl-4-aminobutylpropylketone; the mixture is shaken up with ether, which removes the derivatives and the methyl coniin, and the latter is recovered by shaking out with dilute acid. The ether solution is then dried, concentrated, and treated with light petroleum ether, which precipitates the bulk of the benzoylaminobutylpropylketone. The solution is filtered, evaporated and distilled *in vacuo* up to 220° C., and the residue dissolved in ether and precipitated with petroleum ether, the precipitate being added to the rest of the ketone derivative from which the conicein is recovered. The distillate contains the benzoylconiin from which the alkaloid may be recovered.

Quantitative Examination of Coniin Products.—The methods for the assay of the drug Conium have been described in the chapter on drug assaying. For fluid extracts or tinctures a quantity representing the amount of drug used in the assay should be evaporated on sand or washed sawdust and the procedure carried out as for the drug.

When either the drug or a salt of coniin is present alone in a liquid product, the separation of the alkaloid can be effected very simply by diluting the mixture, rendering alkaline with sodium carbonate and shaking out three or four times with ether. The solvent is then shaken three

[1] Ber., 1905, 38, 3108.

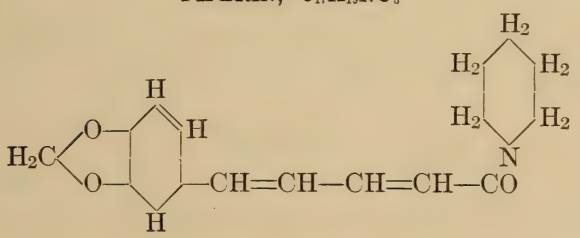
times with dilute hydrochloric acid and the combined acid solutions washed once with ether (discarding the latter), made alkaline with sodium carbonate, and the liberated alkaloid shaken out with three portions of ether. The ether solution is then washed with a little water, filtered into a tared beaker and evaporated with hydrochloric acid, using the precautions given under the assay of the drug.

With tablet triturates and hypodermatic tablets, the simplest procedure consists in putting 10–25 tablets into a large separator, adding water, shaking until the tablets are disintegrated and then adding excess of sodium carbonate. The alkaloid may be then removed by ether and the determination continued as described under liquids above.

In the case of pills or tablets where there is considerable mass and usually a heavy sugar coating, the sample must be ground up in a mortar and triturated three or four times with 95 per cent alcohol, filtering the alcoholic extract into an evaporating dish and evaporating the bulk of the solvent. The contents of the dish are then treated with dilute sulphuric acid and the liquid filtered into a separator, thoroughly washing the dish and filter with dilute acid. From this point the assay follows the directions given under liquids above.

Determination of Coniin in a Mixture of Alkaloids.—As was noted above, coniin will sometimes be found present with the ipecac alkaloids, opium alkaloids, atropin, hyoscyamin, aconitin, and strychnin, and the simplest method of separation is by distillation with steam. In all cases it is advisable to first separate the combined alkaloids from the bulk of the product by ether, using any one of the above manipulations, depending on the class of the material in hand, After obtaining an ether extract, which will contain all the coniin, it is shaken out with dilute hydrochloric acid and the acid transferred to a distillation flask connected up for steam distillation and fitted with a trap to prevent foreign substances from coming over mechanically. The acid solution is made alkaline with sodium carbonate and the distillate received in a flask containing dilute hydrochloric acid. The liquid in the receiver is finally transferred to a separator, made alkaline with sodium carbonate and the assay for coniin completed as usual.

PIPERIN, $C_{17}H_{19}NO_3$



This alkaloid occurs in the fruits of Piper nigrum, P. longum and other species, the first named being the chief source of the commercial pepper products. The dried berries are equal in size to a small pea, externally blackish, reticulated and wrinkled, internally whitish, with an undeveloped embryo. They contain from 4 to 10 per cent of piperin, a soft greenish resin, a volatile oil and the usual vegetable matter contained in leguminous plants.

For medicinal use the oleoresin is prepared by extracting the powdered berries with ether and allowing the evaporated extract to stand until a portion of the piperin has settled out, when the soft resinous mass is strained through muslin. Both the oleoresin and the ground pepper are employed as stomachics and stimulants in colic, cholera morbus, flatulence, intermittent fevers, etc., and should be looked for in pills and tablets labeled anti-chill, anti-malarial, carminative, ague and stomach tonic. The alkaloid piperin is seldom used by itself. Oleoresin of pepper will be found in combination with Cinchona bases, arsenic, colocynth, ferrous sulphate, Gelsemium, gentian, ipecac, aloin, and cloves. It has been combined with Prussian blue in chill remedies and occasionally used with strychnin in bitter tonics.

Piperin crystallizes in pale yellow prisms melting 128–130°, almost insoluble in cold water, slightly soluble in ether, and readily soluble in alcohol, chloroform, benzol, and petroleum ether. It is a weak base and its salts formed with mineral acids are immediately decomposed by water. It is easily removed from an acid solution by means of petroleum ether. Its solutions are pungent.

The hydrochloride dissolved in alcohol gives precipitates with alcoholic mercuric chloride, platinic chloride, and aqueous iodine in potassium iodide. The dry alkaloid gives an orange to blood-red color with concentrated sulphuric acid, and an orange-red resin with nitric acid, becoming blood-red when alkali hydroxides are added.

On boiling with alcoholic potash it is hydrolyzed to piperidin and piperic acid.

$$C_{17}H_{19}NO_3 + H_2O = C_5H_{11}N + C_{12}H_{10}O_4.$$

The former substance is a volatile liquid and a strong base, boiling 105°, soluble in water, alcohol, ether and benzol. Piperic acid, on oxidation with permanganate, is converted into piperonal, which has the odor of heliotrope, and the formation of this substance by previous hydrolysis of the alkaloid is a test for the presence of piperin.

PIPERIDIN

Piperidin has an unpleasant ammoniacal odor. It boils at 106° C. and is soluble in all proportions in alcohol and water. Its aqueous solu-

tion precipitates metals similarly to ammonia, but the zinc and copper compounds are not soluble in excess. The aurochloride crystallizes from alcohol in leaflets, melting 218–229°, with decomposition, and when obtained from alcohol, the crystals contain one molecule of the solvent and melt at 191°. The picrolonate melts at 142° with decomposition.

Piperidin gives a blue color when treated in aqueous solution (1 drop to 3 mils) with 1 mil of dilute acetaldehyde solution and 1 drop of 1 per cent sodium nitroprusside. The blue color changes through greenish blue to pale yellow. This is a general reaction for secondary amines.

Piperidin reacts with a freshly prepared solution of gallic acid, producing a pale-rose color turning deep yellow; with pyrogallol, a yellow color appears at once, changing to brownish black; with catechol a violet color changing to pink and finally to yellow; with quinol, a yellow to deep brown.

Piperidin reacts with carbon bisulphide to form piperyl dithiocarbonate which crystallizes out of alcohol in lustrous plates, and which, when heated rapidly in a capillary tube, soften at 168° and melt at 172–175° C.

In analytical work one is not concerned with the quantitative estimation of piperin. In the general scheme of alkaloidal separation, the base will appear in the fraction obtained by shaking out the acid solution with petroleum ether. The pungency of the residue will immediately suggest piperin, and it may be further identified by its color tests, melting-point, and odor test.

If it is contaminated with resinous matter the mass should be dissolved in dilute alkali and shaken out with petroleum ether to remove the piperin. The alkaloid must then be further purified by recrystallization from petroleum ether or ether before a determination of its melting-point and color tests are made. Unless the substance is nearly colorless the color reactions will be unsatisfactory.

The pungent principle of capsicum will also appear at this point, but it is readily distinguished from piperin by its failure to give the same color and odor tests.

ALKALOIDS OF THE BETEL-NUT PALM

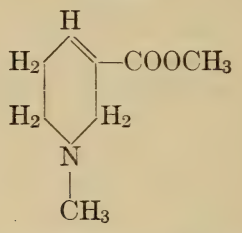
Arecaidin, $C_7H_{11}NO_2$ or $C_8H_{11}NO_2$.
Arecolin, $C_8H_{13}NO_2$.
Guvacin, $C_6H_9NO_2$.
Arecain, $C_7H_{11}NO_2$.

The four alkaloids occur in the betel-nut, the fruit of Areca catechu (Palmæ). The plant is native in Sunda and is cultivated in the Philippines and India. The fruit is used extensively as a masticatory. It

is a grayish-brown, hard, conical-shaped seed, with numerous spiral reddish veins.

A fluid extract of the drug is astringent and has vermifugal properties. It is used for the expulsion of tape-worm and in veterinary practice, and the alkaloids may be anticipated in liquid products advertised as vermifuges. It is administered in the liquid form as the properties desired are credited to arecolin, which is volatile. Arecolin hydrobromide is used as a cathartic and anthelmintic in veterinary practice and as a myotic in the human eye. Arecolin-eserin is a mixture of equal parts of arecolin hydrobromide and physostigmin sulphate, it exhibits the combined therapeutic properties of the components and is employed as a myotic and subcutaneously as a cathartic in veterinary practice.

Arecolin



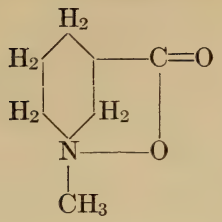
Arecolin is the chief alkaloid of the nut and on which its therapeutic activity depends. It is closely related to the other bases of this group in composition, but differs markedly in chemical and physical properties. It is a methyl ester of a tetra-hydro derivative of trigonellin.

Arecolin is an oily liquid, colorless and odorless, volatile with steam, strongly alkaline and boiling 209°. It is soluble in water, alcohol, ether, and chloroform.

Mayer's reagent gives a yellow, oily precipitate which soon crystallizes, iodine gives a brown oily precipitate, and picric acid a resinous precipitate, both of which finally crystallize. With potassium-bismuth iodide (Dragendorff's reagent) a fine crystalline pomegranate red precipitate is obtained. The aurochloride is a yellow oil. No precipitates result with platinic or mercuric chlorides or tannic acid, but a platinochloride is precipitated when mixed alcoholic solutions of arecolin hydrochloride and platinic chloride are treated with ether. The sulphate, nitrate, acetate, hydrochloride and hydrobromide are well-defined salts, the latter being the one of commercial importance and official in the German Pharmacopœia.

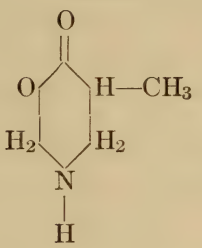
On saponification with acids or bases the oxymethyl group is split up and arecaidin results. The converse takes place on treating arecaidin with methyl alcohol and hydrochloric acid, and if methyl alcohol is replaced by ethyl alcohol, homoarecolin is formed, which resembles arecolin very closely.

Arecaidin



Arecaidin crystallizes in plates containing 1 molecule of water, and when dehydrated melts with decomposition at 223–224°. It is readily soluble in water, with difficulty in alcohol, and insoluble in ether, chloroform, and benzol. It forms salts with both acids and alkaloids. Its aqueous solution has a slightly acid reaction. It has no physiological acitivity.

Guvacin



Guvacin crystallizes from alcohol in shining crystals which melt with decomposition at 271–272°. It is readily soluble in water and somewhat soluble in dilute alcohol, but insoluble in absolute alcohol and the other organic solvents.

Arecain

Arecain is *n*-methyl guvacin. It crystallizes with 1 molecule of water, which it loses at 100° and melts with decomposition at 213–14°. It solubility resembles that of guvacin.

With the exception of arecolin none of these alkaloids is of importance in drug analysis. Arecolin may be separated from them by its solubility in the organic solvents and is markedly distinct from them in being volatile with steam.

PILOCARPUS (JABORANDI) ALKALOIDS

Pilocarpin, $C_{11}H_{16}N_2O_2$.
Isopilocarpin, $C_{11}H_{16}N_2O_2$, a stereoisomer.
Pilocarpidin, $C_{10}H_{14}N_2O_2$.
Jaborin, $C_{11}H_{16}N_2O_2$.

These alkaloids occur in the leaflets of different species of Pilocarpus

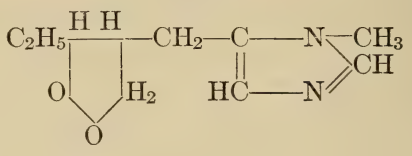
chiefly in P. microphyllus, P. jaborandi, P. pennatifolius, P. racemosus, of the family Rutaceæ.

The botany of Pilocarpus has been for some time in a chaotic state. The distinguishing features of the leaves are often difficult to determine. The leaflets of two dozen species are sold commercially, some of which are devoid of alkaloidal content. The name "Jaborandi," which is applied to the drug in the trade, and unfortunately to some extent in science, has virtually no meaning. It is attached to all species of Pilocarpus regardless of their medicinal value. Among the trade the drug is denoted as Pernambuco, Paraguay, Maranham, Ceari, Aracati, Rio Janeiro Jaborandi, and others, and these designations all relate, either to the country in which the drug is grown, the port from which it is shipped into commerce, or they are the common names applied by the people, and the terms are meaningless considered in relation to the species.

The leaflets are emarginate and the surface presents a multitude of transparent dots discernible when the leaf is held between the eye and a strong light, these two features distinguishing the drug from others of similar general appearance and from adulterants. They do not, however, distinguish a valuable species of Pilocarpus from a worthless variety.

Preparations of pilocarpus and Pilocarpin are used to a limited extent as expectorants, aperients, diaphoretics, sialagogues, sudorifics, and galactagogues; in hair tonics, remedies for Bright's disease, and in eye remedies for contracting the pupil. As a general thing the drug or the alkaloids are dispensed by themselves, and, except in the case of hair tonics, one will rarely meet with mixtures. Tablets of pilocarpin nitrate and hydrochloride are the forms in which the alkaloid is used, and the drug is used as its fluid, solid or powdered extract.

Pilocarpin



This alkaloid is usually seen as an oily syrup, as it is very hygroscopic, but it may be obtained in the anhydrous condition, and, when quite pure, is crystalline. It is readily soluble in water, solutions of caustic alkalies, alcohol, chloroform, and benzol, and less so in ether. The solutions of the alkaloid and its salts are dextro-rotatory, $(a)_d = +100.5°$. It is converted into isopilocarpin by heating the hydrochloride for half an hour at 204–205°, or by distilling the free base *in vacuo*. An acid solution gives precipitates with Mayer's reagent and iodine, but none with potassium ferrocyanide nor tannic acid. Picric acid gives a precipitate in concentrated

solution acidulated with hydrochloric acid. It may be shaken out from weak ammoniacal solution but not from a solution of caustic alkali. Bromine acts on it at high temperatures giving bromcarpinic acid, $C_{10}H_{15}N_2O_4Br$, melting 209°.

Pilocarpin gives few color reactions on which any reliance can be placed, and none with the commonly used reagents. Helch's reaction gives good results and may be applied to a solution of the hydrochloride. From .01 to .02 gram of the salt is dissolved in a little water, 1–2 mils of an acid solution of hydrogen peroxide is added, followed by 2 mils of benzol and a few drops of a 0.3 per cent solution of potassium bichromate. On shaking, the benzol layer will become purple to blue in the presence of pilocarpin. Pyridin and quinolin both give a violet coloration under the same conditions, but the color soon fades; apomorphin gives a violet changing to green on separating the benzol and addition of dilute stannous chloride; antipyrin gives a blue color, distinguishable from that of pilocarpin by shaking the benzol layer with water containing a trace of hydrochloric or sulphuric acid, and treating this acid layer as before with peroxide, bichromate, and benzol, when the color will be regenerated, which is not the case with pilocarpin. Apomorphin is usually indicated long before it is finally separated from a mixture by the green color imparted to the solution, and the reddish-violet color imparted to the solvents, on shaking out from alkaline solutions.

Pilocarpin or its hydrochloride reduces calomel when intimately mixed with it, the reaction being similar to that produced by cocain.

Pilocarpin forms certain well-defined salts, the nitrate melting 178°, the hydrochloride melting 204–205°, the hydrobromide melting 185°, the picrate melting 158–160°, the aurochloride melting 100°.

Pilocarpidin

This body occurs in very deliquescent crystals, strongly alkaline, soluble in alcohol, chloroform, and water and slightly so in ether and benzol. It is optically active. It possesses acid properties and unites with alkalies to form salts which are readily decomposed by carbon dioxide.

Isopilocarpin

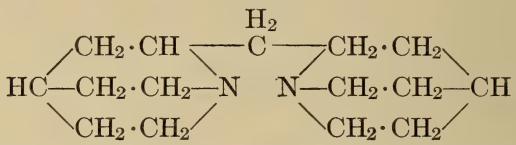
This alkaloid bears a close resemblance to pilocarpin and its stereoisomer. It has $(\alpha)_D = +42.8°$. It forms the same well-defined salts as pilocarpin, the nitrate melting 159°, the hydrochloride melting 127°, and hydrobromide melting 147°.

Quantitative Determination.—As pilocarpin will seldom be found mixed with any other alkaloid, its determination may be accomplished without difficulty. In the case of tablets of pilocarpin hydrochlorate or nitrate, about twenty-five should be transferred to a separator, disinte-

grated with a little water, then ammonia added and the alkaline mixture shaken out three times with chloroform. The combined chloroform extracts are then shaken out with three portions of normal hydrochloric acid, and the pure alkaloid finally removed from this latter solution with chloroform after adding excess of ammonia.

Pilocarpin may be determined in hair tonics by first removing the alcohol by distillation or evaporation, adding ammonia, shaking out the alkaloid with chloroform, and purifying it as in the case of tablet determination. In case the first manipulation with chloroform is difficult, owing to emulsification, Prolius mixture can be substituted to advantage, and in the event of such a solvent being used it must be removed by evaporation before proceeding with the purification.

SPARTEIN $C_{15}H_{26}N_2$



This alkaloid occurs in the broom plant, Cytisus scoparius (Fabaceæ), the tops of which are used medicinally. It is also reported by Willstatter and Marx as occurring in Lupinum luteus and L. niger. The alkaloid is usually applied in the form of its sulphate, it is laxative and diuretic, is employed in dropsy due to the heart, and in anasarca of chronic kidney disease, and may be expected in cardiac pills and tablets. Spartein sulphate is sold alone in the form of tablet triturates and hypodermatic tablets, and in heart tonic mixtures in conjunction with Cactus grandiflorus, digitalin, strychnin, nitroglycerin, and strophanthin or with Strophanthus, caffein, and codein. Spartein has been used as an ingredient of treatments for the drug habit combined with morphin sulphate, heroin, caffein, pilocarpin, and carbolic acid.

Pure spartein is a colorless, oily liquid, heavier than water, with an odor resembling anilin, and a very bitter taste. It darkens and thickens on exposure to air. When pure it boils about 320° C. under normal pressure. It is lævorotatory in absolute alcohol, readily soluble in alcohol, ether, chloroform, and petroleum ether, slightly soluble in water and insoluble in benzol.

It gives no characteristic color reactions with mineral acids. It is precipitated from solutions of its salts by a number of alkaloid reagents, and some of the salts obtained are crystalline with definite melting-points, the platinochloride melts 244–257° with decomposition, the aurochloride melts 175–180° with decomposition, the picrate melts 178–180°. It gives precipitates with Mayer's and Wagner's reagents, cadmium iodide,

sodium phosphomolybdate, silico-tungstic acid, potassium iodide, bromine water, etc.

Spartein is volatile with steam. A piece of moistened red litmus paper held over a vessel containing the free alkaloid is gradually turned blue.

An ethereal solution of iodine added to a solution of spartein in ether causes the precipitation of a black periodide. This substance may be dissolved in boiling alcohol and on cooling separates out in the form of green needles. An orange-red coloration is produced when spartein is treated with a drop of ammonium sulphydrate. An ethereal solution of spartein to which about 20 mg. of dry sulphur has been added, yields an abundant bright red precipitate on passing hydrogen sulphide. Coniin, when treated in the same way, gives an orange turbidity.

Spartein is readily oxidized by calcium hypochlorite, hydrogen peroxide, silver oxide, etc., and yields a series of oxysparteins.

The ordinary form in which spartein occurs in the market is the sulphate, $C_{15}H_{26}N_2 \cdot H_2SO_4 + 5H_2O$, which is a slightly hygroscopic salt, readily soluble in water and alcohol.

When spartein is added to ferric chloride and potassium thiocyanate which have been spotted out on a porcelain plate and dried. a violet to reddish shade is obtained.

When spartein hydriodide is heated with methyliodide two isomeric iodomethylates are formed. The hydriodides of these are decomposed by heat into methyliodide and spartein hydriodide, the latter being the same substance in both cases. Iso-spartein hydriodide, when treated with sodium carbonate, gives the free base which is an oil boiling at 177–179° C. at $16\frac{5}{10}$ m., insoluble in water, but soluble in the ordinary organic solvents, rotation $(a)_D = 25.01$, specific gravity 1.02793 at 17° $nd = 1.53319$ at 17°. It resembles spartein in all its reactions.

Valeur[1] reports the isolation of a volatile alkaloid from the mother liquors from the crystallization of commercial spartein sulphate. This base, to which the name genistein, $C_{16}H_{28}N_2$, is given, melts 60.5° and boils at 177–178° at 22 mm. It does not reduce permanganate. It forms a picrate melting 215° and a platinochloride containing water which is lost at 110°, the anhydrous substance decomposing at 225° without melting.

In the systematic scheme of alkaloidal analysis, spartein will appear in the petroleum ether shake-out from ammoniacal solutions. If it is suspected by preliminary tests, it may be readily separated from other alkaloids with which it may occur by a steam distillation and its identity established beyond question by appropriate tests, the most characteristic of which have been described above.

To determine spartein, when it occurs as the sulphate alone in tablets, the sample should be disintegrated with water in a separator, treated

[1] J. Pharm. Chim., 1913, 8, 573.

with excess of ammonia and shaken out three times with ether; the ethereal solutions are combined and shaken out with dilute hydrochloric acid, and the acid solution treated with excess of ammonia and shaken with ether; the ether, which now contains pure spartein, should be filtered into a tared flask and subjected to dry hydrogen chlorid gas in slight excess, the ether carefully evaporated and the residue warmed and subjected to a gentle blast to remove the excess of acid and then dried in a vacuum desiccator.

In the case of mixtures the alkaloids should first be separated in a crude way by shaking out an ammoniacal solution with ether and chloroform, and then extracting this ether solution with dilute sulphuric acid; the acid solution is transferred to a distilling flask fitted up for steam distillation, the bases liberated with fixed alkali and the spartein distilled over into dilute acid, from which it may be separated as previously described. Strychnin may be determined in the solution remaining in the distilling flask by shaking out with chloroform. Codein, if present, would probably be partly decomposed.

Spartein can also be determined as the silicotungstate. The alkaloid, separated from the rest of the mixture in which it occurs by suitable means similar to that above described, is finally brought into solution in very dilute hydrochloric acid and precipitated by a 10 per cent solution of silicotungstic acid or its potassium salt. The precipitate may be filtered onto a Gooch and dried at 100°. It has the composition SiO_2, $12WO_3$, $2H_2O$, $2C_{15}H_{26}N_2+7H_2O$.

LOBELIN

Lobelin is an alkaloid of Lobelia inflata (Lobeliaceæ), Indian tobacco, the leaves and tops of which furnish the drug which is used extensively in asthma remedies. There are other species of Lobelia which are used medicinally, L. cardinilis, cardinal flavor, and L. syphilitica. The constituents of these subsidiary drugs have not been determined, the first named has been used as an anthelmintic and the latter as an antisyphilitic.

Extract of lobelia and lobelin sulphate are employed medicinally. The extract will be found with Sanguinaria and skunk cabbage, in fluid extract lobelia compound, and in tablets and elixirs recommended for asthma and croup where it is mixed with bromides and iodides, nitroglycerin and Euphorbia pilulifera.

The crude alkaloid has an odor suggestive of honey and tobacco, but is odorless and colorless when pure. It is a volatile, amorphous base, permanent in the air, slightly soluble in water, but dissolving in all the ordinary organic solvents including petroleum ether. As ordinarily extracted from mixtures or the drug it will be obtained as a yellow syrup.

It is precipitated by the usual alkaloidal reagents and gives a very insoluble compound with tannic acid.

Sulphuric acid gives a red color and nitric acid yellow. When warmed with 10 per cent alkali containing 4 per cent permanganate, benzoic acid is formed, which may be separated by filtering, acidifying, and shaking out with ether.

Lobelin sulphate is hygroscopic.

In the usual scheme of medicinal analysis lobelin will appear in the fraction obtained on shaking out the alkaline solution with petroleum ether. When the solvent is evaporated the alkaloid will be left as a yellowish oily or syrupy liquid having the characteristic odor above mentioned. Residues of lobelin should not be heated after the solvent is evaporated on account of the volatility of the base. This property may be used to advantage in separating lobelin from sanguinarin in case it is desired to test for both in the same residue. They both give a red color with sulphuric acid, and while lobelin would probably be indicated by its odor, the presence of sanguinarin could only be ascertained with certainty by removing the lobelin by distillation. It may be observed, however, that while lobelin may be to a considerable extent removed from an alkaline solution by petroleum ether, very little sanguinarin will come out at this point.

The analyst should look carefully for lobelin in asthma, catarrh, and hay fever cures, especially in those which are advertised extensively to the laity. It is probably employed to a larger extent than is credited owing to the fact that it would be easily lost or overlooked.

CYTISIN

Cytisin occurs in a number of minor drugs, among which may be mentioned Baptisia tinctoria (Fabaceæ), wild indigo, used principally as an antiseptic in washes and ointments; Cytisus laburnum, false ebony, which has been recommended in whooping cough, vomiting, bronchitis, and asthma; Euchresta horsfieldii, a Javanese pea used as a contra-poison by the natives; Genesta tinctoria, used as a cathartic and sometimes as a diuretic in dropsy; and in several species of Sophora and Ulex. It is identical with several alkaloids to which formerly different names were applied, ulexin, baptitoxin, and sophorin.

B. tinctoria is probably the only drug which the analyst will encounter in ordinary practice. With the oils of eucalyptus and gaultheria, boric acid, menthol, and thymol it is used in the composition of antiseptic washes of the type resembling "listerine."

Cytisin, $C_{11}H_{14}N_2O$, is a diacid base readily soluble in water, alcohol, and chloroform, but only sparingly in ether or petroleum ether. It crystallizes from alcohol in prisms which melt 152–153° or at 156° when

thoroughly dried; it is lævorotatory and strongly alkaline, easily displacing ammonia from its salts. According to Mullikin it may be removed from acid solution by means of chloroform. It may be sublimed unchanged in a vacuum. Its salts are crystalline and in some cases two types have been prepared. The aurochloride melts 212–213° and is very insoluble. Two platinochlorides are known and are much more soluble than the gold salt. The compound with mercuric chloride is characteristic. It gives precipitates with the usual alkaloidal reagents.

Cytisin gives a red color with ferric chloride which is very characteristic and sensitive even with minute amounts. The red color is destroyed by hydrogen peroxide, and on warming the liquid a blue color is produced. Sulphuric acid added to cytisin gives no color reaction, but on adding thymol and warming a yellow color appears, soon becoming red. Bichromate added to a sulphuric acid solution produces a yellow to brown color. Nitrobenzol containing a trace of nitrothiophen colors the alkaloid violet red.

In the general scheme of alkaloidal analysis cytisin will be found in the fraction obtained by shaking out the alkaline solution with ether, though probably the greater portion will be subsequently removed on shaking out with chloroform.

DELPHINIUM BASES

Extracts of the seeds of Delphinium staphisagria (Ranunculaceæ), stavescare from Southern Europe, and of D. consolida, the common field larkspur of the United States, are employed to a limited extent as medicinal agents. Another species, D. urceolatum, growing in the United States, is sometimes substituted for D. consolida. Stavescare is a powerful emetic, narcotic, carthartic, and vermifuge as well as a parasiticide. It is prescribed in various disorders of the urinary tract, including temporary enlargement or irritation of the prostate, and may therefore be suspected in any remedy recommended for such ailments. It is used externally for eczema and for destroying lice and itch mite.

Larkspur is used principally as a parasiticide for destroying crablice and vermin infecting the scalp.

The bases of D. staphisagria which have been definitely established include delphinin, delphisin, and probably delphinoidin. D. consolida may contain some or all of these bases. Keller[1] obtained a crystalline alkaloid from the latter drug, which was not identical physiologically with delphinin. He also determined that the commercial delphinin is a mixture.

The alkaloids may be extracted from an alkaline solution by ether,

[1] Arch. Pharm., 248, 463.

and on concentrating and allowing to stand the delphinin crystallizes first in rhombic crystals melting 191–198°; on further evaporation delphisin separates, and then dilphinoidin may be thrown out by adding petroleum ether.

The pure bases do not give characteristic color tests. Reactions have been reported which were obtained with impure residues: thus sulphuric acid containing malic acid produces an orange color, changing gradually to red and finally dirty blue; sulphuric acid and bromine water a violet color; and sulphuric acid and sugar a brownish yellow changing to green on dilution with water.

BASE FROM DUBOISIA HOPWOODII

Duboisia hopwoodii (Solanaceæ), growing in central Australia, is another of those plants like coca and kola which furnishes a drug having stimulating properties enabling its devotees to perform much labor and go long journeys with but little food. The drug is a fine powder composed of the leaves and twigs gathered while the flower is in bloom and put up in various forms of circular mats about 6 in. in diameter. The drug has not been exported medicinally to any extent, but attention is called to it owing to its local use, which may lead to its adoption by the pharmaceutical profession after the manner in which coca and kola were first exploited.

The drug contains a volatile alkaloid which has been called piturin, after the local name of the drug Pituri. Investigation by different workers has been conflicting, some claiming it to be identical with nicotin, others denying this similarity. Senft states that it differs from nicotin in its reactions with platinic, gold, and meruric chlorides, and with iodine. Its aqueous solution does not become turbid on heating, which distinguishes it from coniin.

CHAPTER V

ALKALOIDS DERIVED FROM PYRROLIDIN

THE SOLANUM ALKALOIDS

Atropin, $C_{17}H_{23}NO_3$
Hyoscyamin, $C_{17}H_{23}NO_3$
Scopolamin, $C_{17}H_{21}NO_4$.

In addition to the above three it has been recorded that the drugs bearing these alkaloids contain small amounts of atropamin, belladonin, mandragorin and pseudohyoscyamin. However, their existence is doubtful, the literature on the subject is discrepant and it appears from more extended research that they were mistaken for mixtures in varying proportions of the three alkaloids. Hyoscin, which was formerly reported as a naturally occurring constituent of henbane, has now been virtually relegated to oblivion. Daturin, now called atropin, was probably a mixture of atropin and hyoscyamin; duboisin is now classed as hyoscyamin by some and as scopolamin by others.

This group includes also the artificially prepared homatropin, $C_{10}H_{21}NO_3$, having the composition of a lower homologue of atropin as well as other synthetic derivatives of tropein, which are used more or less in medicine.

The following plants of the Solanaceæ have been found to contain these alkaloids; Atropa belladonna, Deadly Nightshade; Hyoscyamus niger, Henbane; H. albus, H. muticus; Datura stramonium, Thornapple or Jamestown Weed, and other species of Datura; Duboisia myoporoides, Corkwood Elm; Scopolia atropoides or carniolica; S. japonica, Japanese Belladonna; Mandragora officinarum, European Mandrake, Anisodus luridus, and according to some authors in Lactuca sativa and virosa (Compositæ). All parts of the plants contain the alkaloids. The relative proportions of the alkaloids have never been satisfactorily determined owing to the ease with which hyoscyamin is converted to atropin, but the consensus of opinion seems to be that atropin predominates in belladonna, though Rusby states that over one-half the total alkaloid in the commercial root is hyoscyamin according to Gilpin and Langdon, while hyoscyamin and scopolamin are present in greater amount in hen-

bane. Pseudohyoscyamin was reported by Merck in Duboisia myoporoides, but has never been observed in any other species.

The young roots of belladonna are reported to contain scarcely any atropin, only hyoscyamin, while the ripe fruit on analysis contains only atropin. The alkaloidal content varies with the period of their growth. Gunther has shown that the fresh plants contain the alkaloids in the following proportions expressed in parts per 1000.

Atropa belladonna, leaves 2.0; stems 0.4: unripe fruit 1.9; ripe fruit 2.1; seeds 3.3; root 0.6.

Datura stramonium, leaves 0.7; stems 0.2; seeds 2.5; root 0.2.

The drugs used medicinally when ready for market contain the alkaloids in the following percentages:

Atropa belladonna 0.2 to 1.0 per cent, the average being 0.55 to 0.60. The Pharmacopœia requiring the leaves test not less than 0.30 per cent and the root 0.45 per cent.

Hyoscyamus .00 to 0.15 per cent, the standard requirement being .065 per cent.

Scopola somewhat greater than the amount present in belladonna root, the old standard being 0.5 per cent, but the drug is no longer official.

Stramonium 0.2 to 0.4 per cent, the Pharmacopœia requiring not less than 0.25 per cent.

The crude belladonna leaves have been found mixed with those of Scopola and sometimes with a species of Phytolacca; Belladonna root has been largely adulterated with Phytolacca root and the literature records the use of Medicago root and Scopola; Hyoscyamus leaves have been adulterated with Stramonium; and Stramonium has been found adulterated with other species of Datura and also with a spurious Stramonium called "French cultivated." Hyoscyamus muticus is often offered for import as true H. niger.

The substitution of one drug for another or the use of an adulterant may be detected microscopically in powdered products; in liquid preparations the analyst's difficulties become greater, especially where one variety of the Solanaceæ has been substituted for another, though the use of products containing Phytolacca should be more readily detected owing to the entirely different nature of the ingredients in the latter.

Extract of belladonna will be found usually in combination with other drugs, and is employed as an anodyne, a suppressant of secretions, for whooping cough, croup, chronic constipation, incontinence of urine, narcotic poisoning, etc. It is an antigalactogogue, and is a component of many different kinds of plasters. The alkaloid has a wide use as a mydriatic. The drug or its alkaloids are chiefly administered in the form of pills and tablets and a large number of different formulæ have been evolved.

Scopola is used as an anodyne. Hyoscyamus is a deliriant narcotic,

anodyne, antispasmodic, and hypnotic, and is employed chiefly to relieve pain and quite nervous excitement. It is used in asthma, whooping cough, functional palpitation of the heart, chorea, hypochondriasis, mania, etc., and also as a sedative in place of opium.

Stramonium is a powerful narcotic, antispasmodic, and anodyne, and is used similarly to belladonna. It is employed in the powered form as a remedy for asthma.

The extract of Duboisia is used for the same purposes as belladonna, but is claimed to be less of a cerebral excitant and more calmative and hypnotic.

Mandragora is stated by Rusby to be the Mandrake of the Bible; it has properties similar to the other drugs of this family, but will seldom if ever be met with in the course of analytical work.

From the above résumé of the uses of the drugs and alkaloids under consideration an idea may be formed as to the different remedies in which they might be expected

Some of the more important combinations of belladonna and atropin include the following:

Pills. Belladonna and aloes or aloin with Nux Vomica or strychnin to which will often be added Capsicum, ginger, Cascara, ipecac, colocynth, and calomel, one or more in different combinations. In some instances Podophyllum will take the place of the Nux Vomica and again the aloes will be omitted. Belladonna, podophyllum and Physostigma are used together; and belladonna is combined with phosphorus. As a component of neuralgic and idiopathic remedies it occurs with Hyoscyamus, Ignatia, Opium, Conium, Stramonium, Aconite and Cannabis sativa; with salicin, zinc oxide, pepsin and Hydrastis it is used for night sweats. Pills of morphin and atropin are used, and atropin has also been combined with quinin, arsenic, and gentian.

Tablet triturates will be found containing many of the above mentioned mixtures of aloin, belladonna, strychnin, Cascara, Podophyllum, ipecac, etc. Bronchitis mixtures are found containing belladonna, aconite, Bryonia, sulphurated antimony and potassium bichromate, or belladonna, opium, ipecac and quinin. Atropin, morphin, camphor, and quinin are used for coryza. An infant's cough formula contains ammonium chloride, ipecac, opium, Glycyrrhiza, and belladonna. A standard formula for follicular tonsillitis contains belladonna, aconite, Bryonia, mercuric iodide, morphin, sodium salicylate, and methyl salicylate. It is used with nitroglycerin, Strophanthus, and Digitalis in heart tonics; it is combined with picrotoxin alone; rhinitis formulas contain belladonna, camphor, and quinin; throat tablets contain benzoic acid, camphorated opium, Glycyrrhiza and belladonna; and a formula is reported for sciatica containing belladonna, aconite, Colchicum and Cimicifuga.

In the formulas of compressed, sugar-coated and chocolate-coated tablets belladonna or atropin take part in a legion of mixtures, many are repetitions of those above given, but to these may be added the following: with potassium iodide, potassium arsenite, Lobelia, and opium in asthmatic compounds; with sanguinarin nitrate, morphin, antimony, and potassium tartrate, aconite, ipecac, and tar in a cough mixture; with boric acid, benzoic acid, potassium bicarbonate, buchu, Triticum, corn silk, Hydrangea in mixtures for cystitis; with gold and sodium chloride, strychnin, nitroglycerin, Digitalis, and Capsicum for dipsomania; with lupulin, Scutellaria, ergotin and zinc bromide; with saw palmetto, cantharides and cornsilk; with terpin hydrate, wild cherry, guaiac, and camphorated opium; with antipyrin, zinc oxide, and Castanea for whooping cough.

Ophthalmic tablets of atropin sulphate and of homatropin hydrobromate are used considerably. Hypodermatic tablets contain atropin sulphate alone and combined with morphin sulphate, and there is a local anesthetic formula containing atropin sulphate, morphin sulphate, and cocain hydrochlorate.

Elixirs are sold to a limited extent containing aloin, belladonna, strychnin and Podophyllum; and a tonic compound sold in capsule form consists of atropin, beechwood creosote, strychnin, arsenous acid, and cod liver oil.

Belladonna ointment usually has a base of benzoinated lard. Belladonna plasters contain lead oleate, petrolatum, rubber, and sometimes soap, colophony and Burgundy pitch in the base.

Hyoscyamus, in the form of the drug extract, enters into a great variety of different combinations, many of which resemble to a greater or less extent those in which belladonna functionates and, consequently they will not be repeated here. Among the pills and tablets attention will be directed to those which have been found to differ from the formulas given above under belladonna. Hyoscyamus with camphor, Capsicum and morphin in anodyne products; with Podophyllum, colocynth, Cascara, Juglans, Nux Vomica, gentian and Apocynum, also with jalap, leptandra, aloin, gamboge and Capsicum in laxative remedies; in the compound vegetable cathartic of the National Formulary. With camphor, valerian and Opium; with irisin and strychnin; with musk root, valerian, and Cannabis sativa in sedative mixtures; with ammonium chloride, Glycyrrhiza, Tolu, cubeb, senega, and ipecac in bronchial remedies; with calomel, rhubarb, and colocynth; with morphin hydrochloride, Cannabis sativa, nitroglycerin, Capsicum, and peppermint in chlorodyne; with ferrous lactate, cinchonin sulphate, arsenous acid, and strychnin; with sodium bromide, acetanilid, and digitalin in hypnotic compounds; with acetanilid, camphor monobromated, sodium salicylate, and Gelsemium for migraine; with sodium bromide, caffein, acetanilid, and morphin for

neuralgic headache; and with opium, Hamamelis, tannic acid, thymol helonias, salicylic acid, boric acid, alum, and eucalyptol for topical use in leucorrhea.

Scopolamin, hydrobramate (Hyosin.) hyoscyamin, and Hyoscyamus extract individually occur in tablet triturates, and the alkaloidal salts occur in hypodermatic tablets.

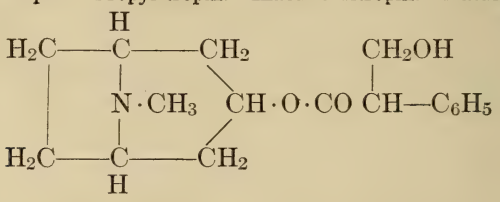
The liquid products are not numerous and are usually elixirs; thus we have a formula embracing chloral, potassium bromide, Cannabis sativa, and Hyoscyamus, and another with the same ingredients including morphin; again a product of the nerve tonic type composed of skullcap, hops, Hyoscyamus, valerian, ammonium bromide, and coca.

Scopola resembles belladonna very closely in medicinal and physiological action but is not used to the same extent. It has been largely employed in the manufacture of plasters and is also the source of most of the commercial scopolamin (hyoscin) salts.

Stramonium occurs in the pill formula mentioned under belladonna which is used for neuralgia idiopathic, but its greatest field is in asthma powders, pastilles, and cigarettes. In powders it occurs with Grindelia robusta, Pilocarpus, Eucalyptus, coca, Digitalis, cubeb, cascarilla, and potassium nitrate; in pastilles with benzoin, Pilocarpus, charcoal, and potassium nitrate; and in cigarettes with cascarilla, Lobelia, and mullein.

Treatments for the drug and liquor habits often contain scopolamin, and with this alkaloid may occur morphin sulphate heroin, caffein, spartein, Pilocarpus, and carbolic acid,

Atropin. Tropyl-tropin. Inactive Atropin. Daturin.



Pure atropin forms tufts or groups of colorless or white lustrous needles or acicular prisms, crystallizing in this way from alcohol or chloroform. In commerce it often occurs as a crystalline or nearly amorphous yellowish powder, and the commercial article usually contains hyoscyamin, from which it may be freed by treatment with dilute alcoholic alkali at a temperature of 110° for five or six hours, until there is no further change in its optical activity. Pure atropin is without action on polarized light. Hyoscyamin is its stereoisomer, being the lævo modification, while atropin is the racemic form. The separation of the latter has not as yet been effected, although the constituents have apparently been synthesized.

It is a strong poison and is used largely in medicine on account of its mydriatic and other properties. Its property of dilating the pupil of the eye is used to confirm its presence. The pure alkaloid melts 115–116° C., while the commercial substance containing more or less hyoscyamin, melts from 104 to 114°.

It is sublimable, almost unchanged; and gradually loses weight when heated to 100° C. It is somewhat volatile with steam.

It is readily soluble in alcohol, chloroform, carbon tetrachloride, and toluol, less so in ether and only slightly soluble in petroleum ether and carbon bisulphide. The proportions given in the literature for its solubility vary over wide limits.

It is not removed by immiscible solvents from solutions acidulated with mineral acids, but from solutions made acid by tartaric acid it is stated that ether and chloroform will remove it.

Its aqueous solution is alkaline to litmus and reddens phenolphthalein, the latter property being almost exclusively characteristic of atropin and its isomers among the other alkaloids.

Atropin is precipitated by Mayer's reagent, iodin in potassium iodide, potassium-bismuthous iodide, potassium-cadmium iodide, phospho-molybdic and phosphotungstic acids, tannic acid; alcoholic picric acid yields a precipitate having a characteristic form, valuable in microscopic detection, and a saturated solution of bromin in hydrobromic acid or alcohol produces a precipitate in dilute solutions, amorphous at first, but soon becoming crystalline and highly characteristic. No precipitates are given with potassium iodide, sulphocyanide, ferro, and ferri-cyanide, nor chromate.

Gold chloride produces a very characteristic precipitate with atropin, in fact the gold chloride compound furnishes the best test for distinguishing between this alkaloid and the other solanum bases. It is thrown down from dilute solutions as an amorphous or oily precipitate which gradually becomes crystalline, and has a well-defined form under the microscope. It melts under hot water and is deposited from its solution in boiling water acidulated with hydrochloric acid in minute crystals which are lusterless after drying at 80° and melt at 135–138°. Hyoscyamin aurochloride retains its luster when dry and melts 160–162°; scopolamin aurochloride melts 198–199°, and homatropin aurochloride 142–145°.

Atropin picrate melting 174.5–175° C. is prepared by adding a few mils of a saturated solution of picric acid to a fairly concentrated solution of the alkaloid in dilute hydrochloric acid. After washing with water, the precipitate should be recrystallized from dilute acetone.

Bromine water in aqueous hydrobromic acid produces characteristic crystals even in very dilute solution. These crystals when viewed under the microscope furnish an excellent test of identity.

With platinic chloride atropin gives a powdery, resinous precipitate which balls together and is very soluble in hydrochloric acid. Hence from solutions acidulated with hydrochloric acid it is not thrown down by platinic chloride, a reaction which distinguishes atropin from the great majority of alkaloids and which may be used to a certain extent for separating mixtures. On evaporating a dilute solution of the platinum salt it separates in monochinic crystals which melt with decomposition at 207–208°.

Atropin sulphate is the form in which it usually appears commercially. though this product is rarely chemically pure, containing a trace of hyoscyamin.

The melting-point of this body is given variously from 180 to 191° C. Beilstein states that the commercial article containing hyoscyamin melts at 188–191° and the pure salt free of hyoscyamin at 181–183°.

Atropin and allied bases respond to a number of interesting color and odor tests. Vitali's color reaction is probably the most sensitive and furnishes a very good indication of the presence of these alkaloids. It is easy of application, the alkaloidal residue being first evaporated with concentrated nitric acid, and when dry and cool the product treated with a few drops of strong alcoholic potash, when in the presence of solanum bases a beautiful purple color appears going through the entire liquid and gradually disappearing through a cherry red. The purple color may be again produced by evaporating with nitric acid and treating with alcoholic potash. While this reaction is of great value as an indication of the presence of atropin, it cannot be considered as conclusive proof, as other alkaloids and alkaloidal residues obtained from medicinal products will give the same or very similar test, so similar in fact that when working with small amounts, the distinguishing features are not apparent. Thus strychnin when similarly treated gives a purple color which is permanent, and gradually becomes brownish; yohimbin and alkaloidal residues from yohimbe bark give a purple color, the color being quite fleeting and most prominent on the edges and in thin layers and soon changing to brown; alkaloidal residues obtained from coca leaf will in some instances give a purple color, but pure cocain will not. It is claimed that veratrin will give the same test as atropin, but the writer has never been able to confirm the statement; commercial veratrin gives a fleeting pink color when nitric acid is added, but no purple color developed on subsequently adding alcoholic potash to the evaporated residue; alkaloidal residues obtained from Veratrum viride acted in the same way and in both cases there was noted a strong odor of old beef. Homatropin does not respond to Vitali's test.

Gerrard has described a reaction with mercuric chloride which Allen epitomizes as follows: 0.1 grain of the free alkaloid (extracted from a

salt by ammonia and chloroform) is placed on a watch glass or in a test tube and 20 drops of a 2 per cent solution of mercuric chloride in 50 per cent alcohol gradually added. A red coloration is yielded at once with atropin. Hyoscyamin at first becomes yellow, then darkens a little, and finally, on heating, a well-marked red precipitate is formed. If a large excess of hyoscyamin be used, merely a yellow precipitate is formed, while with a large excess of the reagent no precipitation occurs. Homatropin also yields a red precipitate under the conditions of the test; but hyoscin (scopolamin) gives neither a red nor a yellow coloration or precipitate, and hence is sharply distinguished from the other tropeins. Gerrard found no red or yellow precipitate to be produced by strychnin, brucin, morphin, codein, veratrin, aconitin, coniin, gelsemin, caffein, cinchonin, cinchonidin, quinin, or quinidin; though most of these bodies gave white precipitates, which, in the cases of codein and morphin, became pale yellow on heating. Cocain is also claimed to give a white precipitate (only appearing in strong solutions and soluble on warming) and scoparin a yellow precipitate.

Atropin and the solanum bases yield a leaf-green to olive-green color when treated with a mixture of 1 volume of perhydrol and 10 volumes of concentrated sulphuric acid. Cocain gives an emerald-green shade.

Atropin when warmed with sulphuric acid until liquid is brown and then treated with a drop or two of water gives off odors of rose, orange flower, and melilot, and the addition of potassium bichromate will change this to the odor of bitter almonds.

Atropin evolves ammonia when heated with caustic alkalies. On heating with chromic-acid mixture benzoic acid is formed.

The physiological test is very delicate and may be performed best on a cat's eye with a dilute neutral aqueous solution of the alkaloid or of the alkaloidal residue to be tested. No alcohol nor free acids should be present, and excess of neutral salts are to be avoided, the specimen being best prepared by evaporating either a hydrochloric or acetic solution until most of the acid has disappeared, then cautiously neutralizing with sodium bicarbonate, and finally filtering. Cocain also produces mydriasis, and coniin, nicotin, aconitin, and gelseminin are stated to have a more or less similar effect on the pupil.

From the above description of atropin it will be seen that for forensic work it is necessary for the analyst to consider more than one reaction when reporting an alkaloid suspected of being atropin. If sufficient quantity is obtainable the melting-point of a positively pure residue furnishes excellent proof when corroborated by the melting-points of the aurochloride and picrate, the microscopic appearance of these salts and the physiological test. The presence of cocain would be indicated by the marked odor of ethyl benzoate when the Vitali reaction was performed.

Both dextro- and lævoatropin have been prepared; they have a melting-point of 110–111° and the aurochlorides melt 146–147°.

HYOSCYAMIN

This alkaloid forms lustrous needles melting 108.5° C. It behaves similarly to atropin both chemically and physiologically. The optical activity, melting-point of the aurochloride and characteristic form of the picrate under the microscope serve to distinguish it from the other solanum alkaloids.

In alcoholic solutions its rotation is $[a]_d - 20.3°$ or $-21°$.

The aurochloride does not melt in boiling water, the scales are lustrous and have a melting-point of 159–162° when pure at 165°. The picrate melts 161–164°.

The platinum salt does not separate from dilute acid solution, but on evaporation of an aqueous solution it may be obtained in orange prisms melting with decomposition at 206° C.

Hyoscyamin may be converted to atropin by heating for several hours at 110° or by standing for several hours in alcohol and sodium hydrate.

Dehydrating agents convert it to atropamin and belladonin. On hydrolysis with barium hydrate or hydrochloric acid it gives tropin and tropic acid.

On saponifying hyoscyamin with hot water Merck obtained tropin and active lævorotatory tropic acid. The lævo-tropic acid is the direct saponification product of hyoscyamin; if the saponification is conducted in an acid or alkaline solution the active acid is converted into the racemic form. Hyoscyamin may thus be considered the lævo-modification of atropin. However, an experiment made in 1889 by Ladenburg and Hunt would seem to indicate that the relation existing between the two alkaloids is not so simple as we might suppose. They separated inactive tropic acid through its quinin salt into two active forms. The lævo-acid thus prepared should be identical with that obtained by Merck, since in tropic acid there is only one asymmetric carbon atom. Ladenburg and Hunt on uniting this lævo-acid with inactive tropin obtained a lævo-tropin, which although similar to hyoscyamin, was apparently not identical with it. From this one might conclude that the stereoisomeris mof the two alkaloids is not situated alone in the acid part of the molecule—the tropic acid—but also in the basic part—the tropin.

According to the investigations of Gadamer, however, the tropin in both atropin and hyoscyamin is inactive, and the only difference between the two alkaloids lies in the inactivity in one case and the activity in the other of the tropic acid radicle. Recently Amenomiya states that he has obtained dextro- and lævo-hyoscyamin by the union of *d*- and *l*-tropic acids with tropin.

l-SCOPOLAMIN

Inactive scopolein ester of lævo-tropic acid

Scopolamin crystallizes with one molecule of water and has a melting-point of 56–57° C. It is generally seen in the amorphous condition.

Chemically and physiologically it behaves similarly to the other alkaloids of this group.

It is somewhat more easily soluble in water than atropin and hyoscyamin and dissolves readily in alcohol, ether, and chloroform.

Its rotation in absolute alcohol is reported as being $[a]_d - 13°$ and $-18°$ and in water $-28°$. Pictet states that the hydrobromide rotates $-25° 43'$.

The aurochloride melts with decomposition at 198–199° C. and Allen states that in the anhydrous condition it melts 214° C. The picrate has a melting-point 187–188°.

The crystalline salts are characteristic in the microscopic form.

On hydrolysis, scopolamin yields tropic acid and oscin or scopolin, and it is slowly hydrolyzed in aqueous solution.

By the action of alkalies or alkaline carbonates scopolamin may be converted into an inactive crystalline derivative having one molecule of water and melting at 56° C., the gold chloride of which melts at 201° or 208°. In commercial scopolamin hydrobromid Hesse found an inactive alkaloid called atroscin and which is the dihydrate of scopolamin. It melts at 38–38°. Atroscin is also found in the roots of Scopolia atropoides. It may be formed when inactive scopolamin is dried over sulphuric acid and then heated to 80° C., the residue dissolved in absolute alcohol, and a few drops of water added.

The anhydrous atroscin melts at 82–83° according to Pictet.

Atroscin can be converted into isoscopolamin by inoculating an atroscin solution with a crystal of isoscopolamin and the reverse transformation has been effected. Further atroscin may be changed to isoscopolamin if the hydrobromide of the former is prepared, the base again freed from this and crystallized from an aqueous solution of definite concentration at 0°. Both atroscin and isoscopolamin are decomposed by alkalies into tropic acid and scopolin.

In order that the relations of these various scopolamin derivatives to one another may be more clearly represented Wolffenstein proposes the following nomenclature:

The inactive anhydrous alkaloid, $C_{17}H_{21}NO_4$, *i*-scopolamin.

The inactive alkaloid containing one molecule of water (isoscopolamin), *i*-scopolamin monohydrate.

The inactive alkaloid containing two molecules of water (atroscin), *i*-scopolamin dihydrate.

DERIVATIVES AND PRODUCTS OF HYDROLYSIS

Atropamin, $C_{17}H_{21}NO_2$, is formed when atropin or hyoscyamin are dehydrated with sulphuric acid or the anhydrides of phosphoric acid, acetic acid, etc. It crystallizes from ether in prisms melting at 60–62°, readily soluble in alcohol, ether, and chloroform, but only slightly soluble in water and petroleum ether. It is inactive to polarized heat and has no mydriatic effect. On being heated it undergoes a molecular rearrangement to form its isomer belladonin. Also when warmed with barium hydroxide or with hydrochloric acid there first occurs the same rearrangement, but this is then followed by saponification to atropic acid, C_9N_8O, and tropin. This reaction has been reversed.

On hydrolyzing the solanum bases we obtain the following:

Atropin and hyoscyamin yield tropic acid, $C_9N_{10}O_3$, and tropin, $C_8H_{15}NO$.

Scopolamin yields tropic acid and scopolin, $C_8H_{13}NO_2$.

Allen states that the preferable method for effecting the saponification of the tropeins is to heat the alkaloid with saturated baryta water to 60 or 80° for a few hours Carbon dioxide is n xt passed through the liquid until a drop ceases to give a pink color with phenolphthalein. The liquid is then filtered and the filtrate acidulated with hydrochloric acid and twice shaken with ether. The ether is separated and on evaporation yields the acid product of hydrolysis; on treating the aqueous layer with caustic alkali in excess and agitating with ether the basic product is extracted and may be recovered by separating and evaporating the ether.

When the hydrolysis is effected by an acid, especially concentrated hydrochloric acid, the tropic acid loses the elements of water and atropic acid results, and at high temperatures this is more or less changed into its polymers alpha- and beta-isatropic acid, $C_{18}H_{16}O_2$.

Tropic acid, $C_6H_5CH(CH_2OH)COOH$
alpha-phenyl-beta-hydroxypropionic acid.

The acid crystallizes from hot water in needles or slender prisms and on the spontaneous evaporation of its aqueous solution in tablets which melt 117–118°. It is not volatile without decomposition. It is somewhat soluble in water and dissolves more readily in alcohol and ether. It is optically inactive and without any particular physiological action. When heated with a dilute solution of potassium permanganate benzaldehyde is given off, and on further treatment benzoic acid is produced.

The formula for tropic acid contains an asymetric carbon atom and it should be possible to separate the inactive acid into two active modifications. This separation was effected as previously mentioned by Ladenburg and Hunt by crystallizing the quinin salts. Dextro-tropic acid melts 127–128° and lævo-tropic acid 123–126°.

Atropic Acid, $C_6H_5C=CH_2COOH$
alpha-phenylacrylic acid

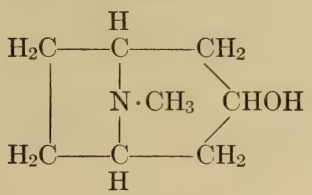
Atropic acid is isomeric with cinnamic acid, but differs from it by its solubility in water (1-692 at 19°, Allen), by its lower melting-point 106–107°, and in not being precipitated by manganese salts from its neutral solutions. It is volatile with steam and boils with partial decomposition at 267° C. It is very soluble in carbon bisulphide. Chromic acid oxidizes it to benzoic acid, and when fused with caustic potash it yields formic and phenylacetic acids. Sodium amalgam reduces it to alpha-phenyl propionic acid and bromin water converts it into brom-phenyl-propionic acid.

Isatropic Acid, $C_{18}H_{16}O_4$

This acid is polymeric with atropic acid and is always formed together with that acid and tropic acid when atropin is heated with hydrochloric acid. It is always formed when atropic acid is crystallized from hot water and especially if the solution has been boiled for some time.

It exists in a number of isomeric modifications, the alpha acid melting at 237° and the beta at 206°. The gamma and delta acids are called truxillic acids, and are described under the products of hydrolysis of the coca alkaloids.

Tropin



Tropin crystallizes from absolute ether in rhombic plates melting 61–63° and boiling 229–233°. It is hygroscopic, readily soluble in water, alcohol, and ether. It is without action on polarized light, has no mydriatic effect, and is much less poisonous than the alkaloids derived from it. It is a strong base, has an alkaline reaction, and forms well-crystallized salts.

The platinum chloride compound forms orange-red monoclinic prisms, easily soluble in warm water, insoluble in alcohol, and melting with decomposition at 198–200°. The aurochloride forms yellow plates melting 210–212°. The picrate is a yellow precipitate crystallizing from hot water in yellow needles, decomposing without melting at 275°.

Scopolin (Oscin), $C_8H_{13}NO_2$

Scopolin crystallizes from petroleum ether or chloroform in prisms, melting at 110°, and boils at 241–243°. It is easily soluble in water and alcohol. It is a tertiary base and optically inactive. It appears to be related to tropin in the sense that a CH_2 group of the latter is replaced by a CO group; it does not, however, give any reaction for ketone.

It is possible to introduce different acid radicles into the tropin and scopolin molecule, thus forming a large number of derivatives known as tropeins and scopoleins. Thus we have products known as benzoyltropein; phenylacetropein, cinnamyltropein; salicyltropein; phenylglycolytropein or homatropin; acetylscopolein, benzoylscopolein, cinnamylscopolein, and many others, whose properties have been studied and constants recorded.

Homatropin, $C_{16}H_{21}NO_3$

$C_8H_{14}NO-COCH(OH)C_6H_5$

This product usually occurs in the form of its hydrobromide. It is prepared artificially and is the tropylester of phenylglycolic or mandelic acid. The base crystallizes from ether in glassy prisms, melting 92–98° according to different authors. Its mydriatic effect is as marked as that of atropin for about twelve to twenty-four hours and then subsides while the effect of atropin will often last a week. It is claimed to be less toxic.

It is readily soluble in ether and chloroform. It is claimed to act similarly to atropin when tested with alcoholic mercuric chloride, but it does not give a purple color when tested by Vitali's reaction. It yields a precipitate with Mayer's reagent and a crystalline precipitate with picric acid, melting 180.5–181.5°. The aurochloride melts 142–145°.

Euscopol

This product is claimed to be inactive scopolamin hydrobromide, differing from the ordinary scopolamin hydrobromide which is stated by the claimants to be a mixture of active and inactive salts.

Distinguishing Tests.—From the descriptions of the individual members of this group the chemist will have no difficulty in distinguishing between the alkaloids. Their melting-points are well defined, their aurochlorides and picrates furnish a ready means for their identification, and their crystalline salts are characteristic under the microscope.

Allen states that Ladenburg employs the aurochlorides to separate the tropeins from each other. The atropin salt is the most insoluble and in fractional precipitation is thrown down first while the hyoscyamin salt is the most soluble. The alkaloids may be recovered by decomposing the

aurochlorides with hydrogen sulphide, adding ammonia to the filtrate and agitating with chloroform and ether.

Formulas where these alkaloids or their salts in the pure form play a part seldom if ever contain more than one individual, so that the chemist will have no occasion to effect their separation. He may, however, be called upon to separate atropin from strychnin, morphin, cocain, and possibly quinin.

We have seen that there are a great variety of mixtures in which the drugs belladonna, Hyoscyamus, scopola and stramonium are used, but here again the number of alkaloids from which the solanum bases must be distinguished are not numerous. Many of the ingredients in the mixtures will be removable from acid solution with immiscible solvents and others may be precipitated by lead salts. If morphin is suspected the product should be treated with sodium hydrate before shaking out with immiscible solvents from alkaline solution.

The ether residue obtained by shaking out an alkaline solution should be the first one examined for this group as petroleum ether extracts but little atropin, most of the cocain if present going into this portion. The Vitali reaction should be tried on a portion and if no purple color is obtained on adding alcoholic potash there is no need of further testing, except to guard against overlooking homatropin. Antipyrin will interfere with this test and will be apparent if present when the mixture is evaporated with nitric acid, a deep purple developing at once and preventing any subsequent reaction with alcoholic potash; and it should be remembered that a whooping-cough mixture occurs containing both antipyrin and belladonna.

Even if on adding alcoholic potash a purple color develops, one is not absolutely certain that atropin, hyoscyamin, or scopolamin are present, as strychnin gives the same color, impure coca bases do likewise, and the alkaloids of yohimbe, exploited now for the same purpose as strychnin, give a purple tint. If cocain is present it would be apparent by the odor of ethyl benzoate, and a test with bichromate-sulphuric acid would show whether strychnin existed. If Vitali's reaction is performed with the chloroform residue in the presence of brucin, it is difficult if not impossible to obtain any purple color owing to the deep shades produced by nitric acid on brucin.

Cocain may be separated partially from atropin, since it is so readily soluble in petroleum ether, two shakings being usually sufficient to remove it, while most of the atropin will remain to go later into the ether and chloroform fractions. Strychnin may be separated from the solanum bases by precipitating it out with platinic chloride in the presence of dilute hydrochloric acid, filtering, and then shaking out the tropeins from alkaline solution. Morphin, of course, will not be removed from a solution alkaline with sodium hydrate, but with opium present one must look for

codein, which fortunately does not interfere with Vitali's reaction, and no trouble need be anticipated from the presence of ipecac and Physostigma alkaloids or quinin.

If it is possible to obtain sufficient of the gold salt and picrate in the pure condition to obtain melting-points, the analyst has an excellent confirmatory test, and the microscopic appearance of the crystalline salts is conclusive.

The question is sometimes asked, How can you distinguish between belladonna and scopola, the latter drug often being used in place of belladonna? If the quantity of alkaloidal residue obtainable is in sufficient quantity, there ought to be no great difficulty in answering the question, for the presence of a considerable amount of scopolamin would be a strong proof that scopola had been used. The separation may be effected by the fractional precipitation of the gold salts and by a method recently described where the hyoscyamin is first thrown out by sodium bicarbonate and after its removal the scopolamin is separated by potassium carbonate; though on the efficiency of this latter method the writer is unable to comment.

Quantitative Methods.—In order to separate and determine the mixed bases when present in the form of the drug extract and when no other alkaloids are present the method described in the Pharmacopœia should be employed.

When the pure alkaloids alone are present, they may be separated by shaking out the alkaline solution with chloroform and the solvent solution evaporated and weighed; due precautions being taken as regards the manipulation, and removal of interfering substances, if present, from acid solution.

When the drugs are mixed with other alkaloid-bearing drugs, pure alkaloids, or substances of a basic nature, one has to study the individual cases to effect a quantitative separation and in some instances the determinations will be difficult if not impossible from an exact standpoint. The fact that the tropeins are held in solution when the platinum salts of the other alkaloids are precipitated in dilute acid solution may be used as a basis of many operations.

Determination of Atropin in Tablets of Atropin Sulphate.—Weigh 25 tablets and introduce directly into a small separator. Moisten with 5 mils water. Add 1 mil stronger ammonia water. Agitate with 25 mils chloroform and allow to stand until separation is complete. Draw off the chloroform into a second separator and repeat the agitation twice more with 25-mil portions of the solvent. After combining all of the fractions, wash the combined chloroformic solutions by agitation with 10 mils of distilled water and allow to stand fifteen minutes. Introduce a pledget of absorbent cotton into the stem of the separator and run off the chloro-

form into a tared dish, but do not allow the wash water to enter the orifice of the stop-cock. Add 10 mils chloroform and when the water has entirely risen to the surface, run off the chloroform into the tared beaker. Wash off the outer surface of the stem of the separator with a little chloroform and then evaporate over a steam or water-bath, using a fan or blower and removing from the bath as the last portions evaporate to avoid decrepitation. Dry to a constant weight in a vacuum desiccator and weigh as atropin. The weight of the atropin may be checked by dissolving the residue in neutral alcohol, adding an excess of N/10 sulphuric acid and titrating back with N/50 potassium hydroxide.

Calculate to atropin sulphate

$$1 \text{ mil N/50 } H_2SO_4 = .005741 \text{ gram atropin}$$

Factor for atropin to atropin sulphate 1.1695.

BELLADONNA PLASTER

U. S. P. Method

Introduce 10 grams of Belladonna plaster into a 100-mil flask. (If the plaster is spread on fabric, cut the portion to be assayed into strips, weigh it accurately, and introduce into the flask.) Now add 50 mils of chloroform, and shake the mixture until the plaster is dissolved. Pour the chloroform solution into a 250-mil beaker and wash the cloth upon which the plaster was spread with two portions of 25 mils each of chloroform, adding the washings to the chloroform solution in the beaker. Then wash this cloth with 80 mils of alcohol containing 1 mil of ammonia water and pour the washings into the chloroform solution in the beaker. Stir the mixture gently and allow it to stand until the rubber has separated into a compact mass. Dry the cloth upon which the plaster was spread, weight it, and subtract its weight from the original weight of the plaster. Pour the chloroform-alcohol solution into a 350-mil separator, rinse the beaker and rubber with 10 mils of alcohol and add the rinsing to the separator. Then add to the separator 100 mils of distilled water, rotate until thoroughly mixed and allow it to stand until the liquids separate. Then draw off the chloroform into a second separator containing 50 mils of distilled water, shake it thoroughly and after separation draw off the chloroform into a beaker and pour the aqueous solution into the first separator. Return the chloroform solution to the second separator and shake out the contents of the first separator with two portions of 10 and 5 mils, respectively, of chloroform, adding them to the chloroform in the second separator. *Completely extract the alkaloids* from the chloroform solution by shaking it out repeatedly with weak sulphuric acid. Collect the acid

washings in a separator and add ammonia water until the solution is decidedly alkaline to litmus, and completely extract the alkaloids by shaking out repeatedly with chloroform. Filter the chloroform solution through a pledget of cotton, evaporate it to dryness, and dissolve the alkaloids from the residue in exactly 5 mils of N/10 sulphuric acid V. S., and titrate the excess of acid with N/50 potassium hydroxide V. S., using cochineal T. S. as indicator.

Each mil N/10 sulphuric acid V. S. consumed corresponds to 28.92 milligrams of the alkaloids from belladonna leaves.

Toxicological Testing.—In toxicological work the use of mineral acids should be avoided, the residues and organs being extracted with alcohol in the presence of acetic or tartaric acid. The alkaloids are best obtained by shaking out an ammoniacal solution with chloroform and if impure a second solution and extraction made. Atropin is rapidly absorbed by all parts of the body and distributed in the blood. 0.03 gram atropin after standing twelve years in contact with decomposing blood, beer, and other organic substances can still be detected. In case of suspected atropin poisoning the urine should be carefully examined.

After taking into consideration the pharmacological action if it is possible to ascertain it, one should apply Vitali's test to a portion of the residue, assure himself of the absence of strychnin with another, perform a physiological test on the eye of a cat with another, and obtain a sufficient quantity of the crystalline gold salt and picrate to test under the microscope and obtain melting-points.

To prepare a solution for pharmacological testing proceed as follows: Dissolve the residue in a small quantity of dilute acetic acid and evaporate cautiously over the steam-bath. Add solid sodium bicarbonate in small quantity until no longer acid, then filter into a clean tube or small flask and preserve carefully corked until ready to apply.

ALKALOIDS OF THE POMEGRANATE TREE

Pelletierin, $C_8H_{15}NO$.
Isopelletierin, $C_8H_{17}NO$.
Methylpelletierin, $C_9H_{15}NO$.
Pseudopelletierin, $C_9H_{15}NO$.

These four alkaloids and probably others occur in the bark of the pomegranate, Punica granatum (Punicaceæ). The barks of the root and stem comprise the drug, and the alkaloidal content ranges from 0.2–4 per cent. The bark is also rich in tannin. It is stated that the drug is sometimes adulterated with the root barks of the box (Buxus) and barberry.

Neither pomegranate nor its alkaloids have a very extended use, so the drug analyst will seldom have occasion to identify or determine them.

The drug has been successfully employed for the expulsion of tapeworm and hence should be sought for in anthelmintics.

Pelletierin and isopelletierin may be separated from methylpelletierin and pseudopelletierin by treating an acid solution of the mixed bases with sodium bicarbonate, which liberates the two latter. They may then be removed by a suitable solvent, and the former subsequently liberated by strong alkali. Commercial pelletierin sulphate and tannate are mixtures of all of the pomegranate alkaloids. Pseudopelletierin is the only one of the group that has been carefully studied constitutionally.

Pelletierin

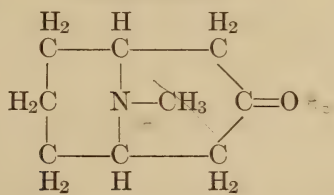
Pelletierin, also known as punicin, is a colorless oily liquid when freshly prepared, but becomes dark and resinous on exposure to air. It has specific gravity 0.988 at 0°, is dextrorotatory, becoming inactive when heated to 100°, and its salts are lævorotatory. It boils at 195° with some decomposition. It is somewhat soluble in water and dissolves readily in alcohol, ether, and chloroform, and slightly in petroleum ether. It gives precipitates with all of the ordinary alkaloidal reagents except platinic chloride. It gives no characteristic color tests with strong acids or oxidizing agents. The residue obtained on evaporating a solution of pelletierin in strong nitric acid gives a strong mousy odor on treatment with alcoholic potash.

Isopelletierin is probably a stereoisomer of pelletierin; it resembles this base in all its properties except that it is inactive.

Methylpelletierin

This is a liquid boiling at 215°, somewhat soluble in water and readily soluble in alcohol, ether and chloroform. Its hydrochloride is dextrorotatory.

Pseudopelletierin



Pseudopelletierin or *n*-methylgranatolin stands in close relationship chemically to the tropa alkaloids. Its oxygen atom is ketonic and it yields an oxime with hydroxlamine. With sodium and alcohol the C=O group is converted into CHOH and methylgranatolin results, melting at 100°. The latter base on treatment with alkaline permanganate loses the CH_3 group and becomes granatolin, melting 134°.

The alkaloid forms prismatic crystals, melting at 48°, inactive, readily soluble in water, alcohol, ether, chloroform, and slightly in petroleum ether.

It is claimed that this alkaloid is not an anthelmintic.

THE COCA ALKALOIDS AND SYNTHETIC ANESTHETICS

The leaves of Erythroxylon coca and E. truxillense (Erythroxylaceæ) contain the following alkaloids:

Cocain, $C_{17}H_{21}NO_4$.
Cinnamyl cocain, $C_{19}H_{23}NO_4$.
Alpha Truxillin, $(C_{19}H_{23}NO_4)_2$.
Beta Truxillin, $(C_{19}H_{23}NO_4)_2$.
Benzoyl Ecgonin, $C_{16}H_{19}NO_4$.
Tropacocain, $C_{15}H_{19}NO_2$.
Hygrin, $C_8H_{15}NO$.
Cuscohygrin, $C_{13}H_{24}NO_2$.

Coca grows in Peru and Bolivia in large quantities and less in Ecuador, Colombia, Brazil, and Argentine. It is also cultivated in the West Indies, Ceylon, Java, Zanzibar, and Australia.

There are two classes of Coca leaves used commercially, the wide and the narrow. The former includes the Bolivia, Huanoco, Munzon, and Cusco varieties and the latter the Truxillo. The wide leaf is the richest in cocain, containing 0.3 per cent 0.8 per cent total alkaloids, 70 per cent to 90 per cent of which is cocain. The narrow leaves run from 0.3 per cent to 0.9 per cent total alkaloids, about 30 per cent to 50 per cent of which is cocain.

Large quantities of crude cocain are shipped into commerce from South America, the material being refined by manufacturers in this country and elsewhere.

An extract of the drug is used in some medicines designed for gastric and intestinal indigestion, malassimilation of food, in cachexias, as a stimulant and general tonic in cases of fatigue and weakness, and to combat the effects of opium and alcohol.

The chief ingredient, cocain, is a local anesthetic and has a wide use. It is employed in surgery, ophthalmic practice, and dentistry, and it was formerly sold to the public in large quantity in the form of asthma cures, hay fever remedies, catarrh snuffs, and dope cures.

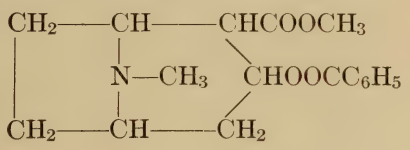
Extract of Coca is often found combined with extracts of celery and kola in form of elixirs, to which other extracts are sometimes added, as Viburnum. In wines it occurs combined with beef extract and with iron. It is also found in combination with malt extract. Prior to the passage of the Food and Drugs Act, Coca extract, with its full content of alkaloids,

was used as an ingredient of popular soft drinks, where it functionated in combination with Kola extract and caffein. The practice ceased several years ago.

Solid extract of coca is an ingredient of some aphrodisiac pills, being mixed with phosphorus, Nux Vomica, and often cinchonidin; and in sedative compounds with valerian, Cannabis sativa, arsenic, strychnin, and occasionally codein.

Cocain in the form of its salts occurs in tablet triturates, dental and ophthalmic tablets, often combined with morphin and atropin, and in various compressed tablets, one of the most important being a throat tablet where it is present with menthol, benzoic acid, eucalyptol, and oil of anise. Again it is combined with borax and potassium chlorate in voice tablets.

Cocain—(Methyl—benzoyl—ecgonin)



Cocain occurs in all Coca leaves. It crystallizes from alcohol in 4- to 6-sided prisms melting at 98° C. It has a slightly bitter taste and numbs the nerves of the tongue. When the tongue or lips have been rubbed with the alkaloid they gradually become numb and feel smooth like ivory until the effect wears away.

It is soluble in 700 parts water at 12° C., 10 parts alcohol, and 4 parts ether, and is also soluble in benzol, toluol, carbon bisulphide, carbon tetrachloride, chloroform, petroleum ether, acetic ether, amyl acetate, acetone, kerosene, aniline, turpentine, olive oil. It is insoluble in glycerin.

It turns the plane or polarized light to the left $[a]_d$—71° 95′.

It is a monoacid base and is readily soluble in dilute acids. It is alkaline to litmus and methyl orange, but does not affect phenolphthalein. Its aqueous solutions are precipitated by ammonia, alkalies and alkali carbonates.

It is precipitated by potassium ferrocyanide, all of the general alkaloidal reagents, Mayer's, Wagner's, tannic acid, phosphomolybdic acid, platinum chloride, gold chloride, by chromic acid on acidulation, by zinc sulphocyanide, by palladium chloride in presence of chlorine water, by mercuric acetate, the precipitate being soluble in excess on standing, but is not precipitated by potassium ferricyanide. It forms with bismuth a double iodide and gives an oily precipitate with potassium bichromate.

Boiling water hydrolyzes cocain to benzoyl-ecgonin and methyl alcohol, while by alkalies it goes to ecgonin and benzoic acid. It is completely

hydrolyzed to ecgonin, benzoic acid, and methyl alcohol by heating for several hours in a pressure flask over the steam-bath.

Cocain gives no characteristic color reactions on which any reliance can be placed when working with small quantities.

The physiological test is characteristic, though of course other substances produce anesthesia, and this alone will not identify cocain.

When moistened with nitric acid and evaporated to dryness, the residue on addition of a few drops of alcoholic potash will give the odor of ethyl benzoate. This odor cannot be mistaken, but it disappears quickly if the amount of the alkaloid is small and hence caution must be used in applying the test. If the odor of the alcohol is confusing, a little water should be added and the contents heated. This is one of the best tests for cocain, quantities as small as .2 mg. being readily detected. The procedure is that of Vitali for the detection of atropin, which gives a beautiful violet color. Tropacocain will also give the ethyl benzoate odor. Hyoscyamin, strychnin, codein, and physostigmin give color reactions and the latter develops an odor resembling phenyl-isocyanide. Delphinin, brucin, and veratrin develop slight odors which, however, cannot be mistaken for ethyl benzoate. Until perfectly familiar with this odor a parallel test should be made using a sample of cocain.

On heating cocain with dilute hydrochloric acid under pressure for four hours over steam, the odor of methyl benzoate can be detected on opening the flask. Tropacocain gives no such odor.

On heating cocain with dilute hydrochloric acid containing a few crystals of salicylic acid, under pressure over the steam-bath, a marked wintergreen odor will be apparent on opening the tube. This test will distinguish cocain from tropacocain.

If 2 to 3 mils of chlorine water are added to a cocain solution and then several drops of 5 per cent palladium chloride solution are added, a red precipitate is formed which is insoluble in alcohol and ether, but soluble in sodium thiosulphate.

On adding 5 drops of a 5 per cent chromic acid solution to a cocain solution, a yellow precipitate will be formed which disappears on shaking. On the addition of 1 mil of concentrated hydrochloric acid a permanent yellow precipitate is formed. If truxillin is present reduction of the chromic acid takes place. Ecgonin, spartein, atropin, caffein, pilocarpin, codein, and morphin do not form yellow precipitates with chromic acid or potassium chromate. Quinin, quinidin, cinchonin, cinchonidin, hydroquinin, apomorphin, brucin, strychnin and veratrin form precipitates with 5 per cent chromic acid if the solutions are neutral, but cocain only gives the precipitate after the addition of hydrochloric acid.

A solution containing not less than 1 per cent cocain gives a copious red precipitate on the addition of potassium permanganate. The behavior

with permanganate serves also to detect an admixture of cinnamyl-cocain and certain other impurities. The presence of these causes an immediate reduction in the cold, the first drop or two of the reagent produces a brown coloration, while the precipitate produced by a further addition is more or less brown instead of a violet red.

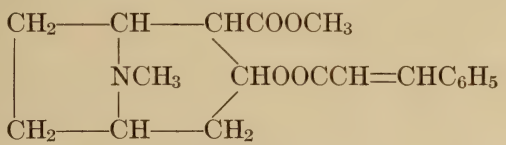
Cocain is removed from an ammoniacal solution by all of the immiscible solvents. In the case of caustic alkalies where the mixture has been heated and subsequently cooled, the cocain will not come out to any extent. However, attempts to make use of this property as a means of separating quinin from cocain have so far led to unsatisfactory results.

Cocain is easily broken down by evaporating it in acid or alkaline solution or even boiling it with water.

Cocain Hydrochloride

Cocain hydrochloride is the principal commercial salt of this alkaloid. It occurs in the form of prismatic crystals or lustrous leaflets and is readily soluble in water and alcohol. If 5 mils of a 1–50 solution in water are treated with 85 mils of water and .2 mil ammonia water (10 per cent), and vigorously stirred with a glass rod, a crystalline precipitate will form within a short time and the supernatant liquid will be clear. This is the customary reaction taking place when the salt is pure and is known as MacLagan's test. The presence of 0.5 per cent of allied coca bases will prevent the formation of a crystalline precipitate and the liquid will retain a milky appearance

Cinnamyl Cocain



Methyl-cinnamylecgonin

This alkaloid is found in all varieties of coca, particularly in that from Java, of which it constitutes one-half the total alkaloids.

It melts at 121° C., is readily soluble in alcohol, benzol, and ether, and sparingly soluble in petroleum ether, but is almost insoluble in water. Its solutions are lævorotatory. It instantly reduces solutions of potassium permanganate and the odor of benzaldehyde is given off on warming.

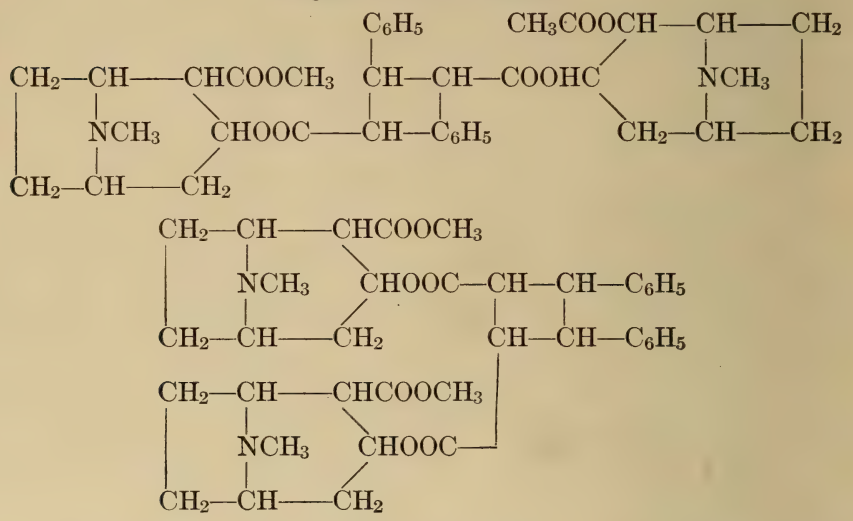
On heating over the steam-bath under pressure in presence of acid it is easily decomposed into cinnamic acid, ecgonin, and methyl alcohol.

It does not give the ethyl benzoate test which is so characteristic of cocain, the ester formed in this case having the odor of ethyl cinnamate.

Furthermore, on evaporating with nitric acid the odor of benzaldehyde is apparent.

Cocain may be readily separated from cinnamyl cocain on account of the ease with which the latter is oxidized by permanganate, in fact experiments conducted by Garsed show that the cocain can be recovered quantitatively.

Alpha and Beta Truxillins



Alpha truxillin, cocamin, isatropyl-cocain, as it is variously called, is amorphous. It melts at 80° C., is little soluble in water and petroleum ether, but soluble in the other organic solvents. Its solutions are lævorotatory. It is quite bitter.

Beta truxillin possesses similar properties, it is amorphous and begins to melt at 45° C. It differs from the alpha by its slight solubility in alcohol.

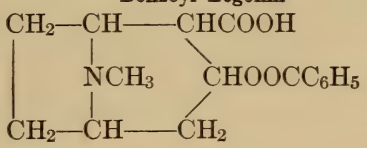
The acid products of hydrolysis, cocaic, isatropic, or truxillic acids are polymers of cinnamic acid and on distillation are converted into this acid. They do not absorb halogens and on oxidation do not yield benzaldehyde, hence they have no double bond. They are much more insoluble in water than either benzoic or cinnamic acids and may be separated from them by simply filtering an aqueous solution which is sufficiently dilute to hold up the benzoic and cinnamic acids.

The truxillins are not oxidized by permanganate and may be separated from cinnamyl-cocain in a manner similar to cocain.

In order to identify the cocain in a mixture of the same with cinnamyl cocain and the truxillins, the solution should be treated with permanganate. The benzoic acid formed in this reaction may be removed by shaking out from acid solution with ether and then the residual solution

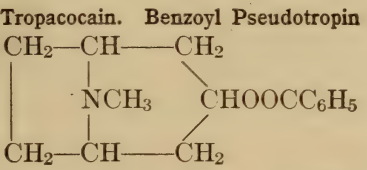
heated for three or four hours in a pressure flask over the steam-bath. By evaporating to a dilution of about 1–400 the benzoic acid will remain dissolved when cooled to 12° C., while the truxillic acid will be almost completely separated. The solution may be filtered and the clear filtrate shaken out with ether, which will remove the benzoic acid formed by the hydrolysis of the cocain. It can then be identified by its melting-point and other characteristic tests.

Benzoyl Ecgonin



This substance exists naturally to some extent and results from the partial saponification of cocain. It is soluble in water and alcohol but only slightly soluble in ether. The hydrous form melts at 90° C. and the anhydrous at 195° C. It is soluble in alkalies.

Tropacocain. Benzoyl Pseudotropin



This alkaloid crystallizes from ether in plates having a melting-point of 49° C. It is insoluble in water, but dissolves in alcohol and follows cocain very closely in solubility in the organic liquids.

On hydrolysis with dilute mineral acids it splits up into benzoic acid and pseudotropin. It gives precipitates with the general reagents for alkaloids.

With potassium bichromate it yields a crystalline precipitate instead of the oily residue given by cocain.

A few drops of a 5 per cent solution of chromic acid precipitates at once a solution of a tropacocain salt. When a mixture of the salts of both cocain and tropacocain are treated with 5 per cent chromic acid the tropacocain is precipitated at once and agglomerates, sticking to the side of the tube. On filtering and adding hydrochloric acid to the filtrate, a copious precipitate characteristic of the cocain compound is formed.

It gives a precipitate with mercuric acetate which does not go into solution again on standing as in the case of cocain.

With potassium ferricyanide it gives a precipitate of needle-like crystals gradually appearing. Cocain does not precipitate with this reagent.

Hesse states that on account of its solubility in dilute ammonia it may be separated from the other coca alkaloids.

Hygrin

This is a liquid having a boiling-point of 193–195° C. It is a tertiary base, contains a N methyl group but no methoxyl. Its oxygen is ketonic in character, since it forms an oxime which can be distilled almost unchanged. It is easily soluble in alcohol, but with difficulty in water, ether, and petroleum ether. It is decomposed by light.

On oxidation with chromic acid, monbasic hygric acid, $C_5H_{10}NCOOH$, results, which crystallizes with one molecule of water and melts at 164°.

It absorbs carbon dioxide from the air and also forms a hydrochloride and a hydroiodide. It gives a well-defined needle-like picrate melting at 148°. (160° Beilstein.)

Lieberman claims that hygrin occurs chiefly in the Cusco leaves, where it is present to about 0.2 per cent.

As obtained from coca leaves hygrin is not a substance of definite composition, but consists of a mixture of liquid bases which can be separated from each other only with difficulty.

To prepare hygrin, according to Lieberman and Cybulski, 200 grams of impure hygrin obtained from Cusco leaves were strongly acidulated with 150 mils 33 per cent hydrochloric acid to decompose the acylecgonin present and boiled for one hour on the water-bath with an air cooler, the acids were separated with ether and then 250 grams concentrated potassium hydroxide (2–1) added, and the bases dissolved out with ether. The ether solution was washed with caustic alkali or with barium hydroxide, the ether then distilled and the residual oily bases fractionated. Hygrin goes over between 92–94° at 20 mm. pressure, or at 111–113° at 50 mm., specific rotation $[a]_D - 1.3°$. The high boiling constituent of the basic mixture consists, according to the authors, of cuscohygrin and β-hygrin.

The presence of hygrin and cuscohygrin in extracts of dried coca leaves is a matter of controversy at the present stage of our knowledge of this class of alkaloids. That they occur in the fresh leaves has been definitely ascertained, and from work done on the extracts of dried leaves it is probable that they exist there also, but further experimental research into the phytochemistry of the drug is needed before the obscure points can be definitely settled.

Dr. Rusby after an extended research on the subject of the coca leaf was satisfied that, before exportation, the drug contained a much higher percentage of alkaloid. It is his belief that during transit the leaves lose some volatile substance, perhaps hygrin.

Cuscohygrin

This is also a liquid of oily nature and boils at 185° C. at 32 mm. It is easily soluble in water, forms a hydrate which melts at 40–41° C., and a well-defined nitrate which permits its separation from hygrin.

It is a di-acid tertiary base with a methyl group attached to each nitrogen.

PRODUCTS OF HYDROLYSIS OF THE PRINCIPAL COCA ALKALOIDS

On heating the alkaloids to 80–100° C. with hydrochloric acid preferably under pressure, or boiling with alcoholic potash they act as follows:

Cocain, $C_{17}H_{21}NO_4 + H_2O = \underset{\text{Benzoyl ecgonin}}{C_{16}H_{19}NO_4} + CH_3OH$

then $C_{16}H_{19}NO_4 + H_2O = \underset{\text{Ecgonin}}{C_9H_{15}NO_3} + C_6H_5COOH$

Cinnamyl Cocain, $C_{19}H_{23}NO_4 + H_2O = \underset{\text{Cinnamyl Ecgonin}}{C_{18}H_{21}NO_4} + CH_3OH$

then $C_{18}H_{21}NO_4 + H_2O = \underset{\text{Ecgonin}}{C_9H_{15}NO_3} + \underset{\text{Cinnamic Acid}}{C_9H_8O_2}$

Truxillin, $C_{38}H_{46}N_2O_8 + 3H_2O = C_9H_{15}NO_3 + C_{27}H_{29}NO_6 + 2CH_3OH$

then $\underset{\text{Ecgonyl cocaic acid}}{C_{27}H_{29}NO_6} + H_2O = C_9H_{15}NO_3 + \underset{\text{Truxillic acid}}{C_{18}H_{16}O_4}$

Tropacocain, $C_{17}H_{19}NO_2 + H_2O = \underset{\text{Pseudotropin}}{C_8H_{15}NO} + C_6H_5COOH$

The ease with which the Coca alkaloids are decomposed is taken advantage of in the commercial field. The mixed alkaloids are hydrolyzed, the resulting acids separated and then the ecgonin converted to cocain.

Ecgonin is a solid substance containing one molecule of water melting at 198–199° C. It is readily soluble in water and its solutions are lævorotatory. It is soluble in ethyl acetate, slightly soluble in alcohol, almost insoluble in ether, and does not dissolve in acetone, chloroform, toluol, carbon bisulphide or carbon tetrachloride.

It acts as a tertiary base, a monatomic alcohol, and a monacid base. It forms quaternary salts, esters, and normal salts with alkalies which are not decomposed by carbon dioxide. Ecgonin solutions are neutral to litmus, a fact which caused Einhorn to suggest that the acid and basic elements in the molecule neutralized each other, yielding a betaine-like structure. At a dilution of 1–500 it is not precipitated by N/100 iodine, but stronger solutions yield precipitates with iodine.

Ecgonin is not precipitated by potassium mercuric iodide, but forms a very insoluble compound with phosphotungstic acid. It is not removed from aqueous solutions by immiscible solvents except possibly to a slight degree by ethyl acetate.

The identity of ecgonin is best established by converting it to cocain and isolating and identifying the alkaloid. The material under examination should be brought into solution, made slightly alkaline with caustic alkali and the alkaloids removed by agitation with Prolius mixture. The

extraction must be continued as long as any substance is removed which will give a precipitate with Mayer's reagent. If the solution is a plant extract or contains any quantity of foreign matter, it is then neutralized with acetic acid and treated with an excess of Howe's basic lead acetate. After filtering, the excess of lead is removed by potassium oxalate, the filtrate evaporated and the residue thoroughly extracted with pure anyhdrous methyl alcohol. The alcohol solution is warmed, subjected to the action of dry hydrochloric acid gas for about ten minutes, heated again and the treatment with hydrochloric acid repeated, this procedure being continued, adding more methyl alcohol if necessary, for about one-half hour. The mixture is then transferred to a larger and long thick test-tube, the alcohol evaporated, benzoyl chloride added, and the tube heated in an oil-bath at 180–200° C. for one-half hour. At the end of this time the tube is cooled and the contents washed out with ether and sodium bicarbonate solution. After agitation with three portions of ether, the combined solvent solutions are shaken out with dilute sulphuric acid, the acid separated, made alkaline with sodium bicarbonate and agitated with low-boiling petroleum ether, which will dissolve any cocain which may have been formed, and on evaporating the solvent the residue can be subjected to the identity tests for that alkaloid.

On boiling with baryta water methylamine is formed.

On treatment with phosphorus pentachloride a molecule of water is lost and anhydroecgonin is formed, which is soluble in water and alcohol but almost insoluble in ether.

On heating with hydrochloric acid, carbon dioxide is given off and tropidin formed.

Several stereoisomers of ecgonin have been prepared synthetically.

Pseudotropin forms crystals melting at 106° C., boiling 241–243° C. Soluble in water, chloroform, alcohol, but sparingly soluble in ether.

By heating with glacial acetic acid and sulphuric acid tropidin results.

The truxillic acids have already been discussed to some extent under the truxillins. They are not volatile with steam, as are both benzoic and cinnamic acids, and are much more insoluble in water, dilutions of 1–40,000 giving a distinct precipitate. Truxillic acid melts at 274°. Iso-truxillic acid melts at 206°.

The acid is nearly insoluble in ether, from which it crystallizes in a form resembling benzoic acid.

The barium salt of alpha-truxillic acid is soluble in water, while that of the beta acid is insoluble.

The alpha acid is obtained in about double the amount of the beta.

The alpha acid on treatment with acetic anhydride and subsequently with a base is converted into an isomeric acid called gamma-truxillic acid.

The beta acid on fusion with alkali is converted to delta-truxillic acid.

IDENTIFICATION OF THE COCA ALKALOIDS

The analyst of galenical preparations will be called upon to detect the presence of cocain in liquid preparations containing extract of coca leaf and in preparations where it is used as a salt of the pure alkaloid, also to differentiate between it and other alkaloids and various anesthetics of synthetic origin.

As cocain is the chief active ingredient of coca leaf, except possibly that of East Indian origin, little difficulty need be experienced in substantiating its presence in products containing the extract. If by chance one is working with a product where the amount of cinnamyl cocain predominates, the fact that this latter alkaloid is in large quantities may be readily ascertained from a knowledge of its properties taken into consideration with those of cocain, and if the cinnamyl cocain is found it may be removed by making use of the permanganate reaction.

As obtained from a drug extract the alkaloidal residue is seldom crystalline, but has the consistency of a thick oil. If the final extraction has been made with low-boiling petroleum ether, the residue will often crystallize on standing overnight. The deposit is usually without color, but it has a characteristic odor. It has no color reactions on which any reliance can be placed, but its character may be readily determined by placing a bit on the end of the tongue and rubbing it gently for about a minute. A sensation of numbness develops gradually, the tongue and often the lips which have been touched by the finger will have a smooth, ivory-like feeling, and the effect will be apparent for some time.

The residue will give the ethyl benzoate test, and by proceeding according to the method of Garsed described on a subsequent page for determining the alkaloids, a separation and identification of the cocain, cinnamyl cocain, and the truxillins may be accomplished. Ecgonin and benzoyl ecgonin are so soluble in aqueous liquids that they are not removed by ether.

Aconitin will also give the ethyl benzoate test, but it is seldom if ever found with coca alkaloids, and the physiological test would establish its presence at once.

From a solution or other preparation where cocain is present in the form of a pure salt, the alkaloid will be obtained, when not mixed with other alkaloids, in a form which is usually crystalline and which gives a sharp melting-point. In all cases the alkaloid should first be brought into a solution slightly acid and free from alcohol. The solution should first be shaken out with ether and chloroform, then made ammoniacal and shaken out with low-boiling petroleum ether. The petroleum-ether solution should be separated, filtered into a small beaker or dish, and evaporated over the steam-bath. The residue, if pure cocain, will give its characteristic reactions.

Tropacocain in the form of its pure salt is used medicinally, though not to any great extent. It may be readily distinguished from cocain by its melting-point, by not giving the methyl salicylate test, by its immediate precipitation by 5 per cent chromic acid from neutral solution, by its precipitation with potassium ferricyanide, and by the permanence of the precipitate formed with mercuric acetate.

Other common alkaloids which might be removed simultaneously from an ammoniacal solution by means of petroleum ether, may be distinguished from cocain as follows:

Coniin and nicotin may be eliminated, as they would almost never occur. However, the white fumes which develop by bringing a drop of hydrochloric acid on a glass rod near the surface of a residue containing them would be an indication of their presence. They are both volatile and would not interfere with the ethyl benzoate test.

Atropin, which often occurs with cocain, would be detected by Vitalis color reaction, at the same time the ethyl benzoate test is performed.

Quinin would be apparent by the intensely bitter taste of the residue, and the presence of cocain will not interfere with the thalleoquin reaction. The physiological test will show the presence of cocain.

Caffein does not interfere with the ethyl benzoate test, and the presence of cocain does not harm the Murexide test for caffein. Moreover, caffein would be removed by previously shaking out the acidulated solution with chloroform, and again it is practically insoluble in petroleum ether.

Morphin, while it is often used with cocain, would not appear in the petroleum ether shake-out.

The distinguishing tests between cocain and the synthetic anesthetics will be described after a consideration of the properties of these substances.

SEPARATION AND IDENTIFICATION OF SMALL QUANTITIES OF COCAIN

If the substance under examination is a solid it should be dissolved in water, if possible, or in normal sulphuric acid: if it contains much drug material and is not readily dissolved in water an extraction with alcohol should be resorted to, water added to the mixture, and the bulk of the alcohol subsequently evaporated. Liquid products, such as sirups, need no prelimimary treatment unless they are very thick or in the form of emulsion; in the former case they should be diluted to about the consistency of a 50 per cent sugar solution, and in the latter some method which will separate the gum and fatty material must be adopted.

Having obtained a clear solution of the substance in question the procedure is as follows:

Transfer the solution to a separator and add a slight excess of ammonium hydroxide. (If the product was originally alkaline it is best to acidify

it and then add a slight excess of ammonia. If a precipitate is formed it should be separated by filtration and the filtrate used for analysis.) Shake out the solution with 50 mils of Prolius mixture (ether 4 parts, chloroform 1 part, and alcohol 1 part), and allow to stand; then collect the clear solvent in another separator and shake out the aqueous solution twice more with the Prolius mixture. Filter the combined solvent solutions through a creased paper into a beaker and evaporate the liquid over a steam-bath, using a fan. Do not allow the residue to dry, but as soon as the last portions of alcohol are driven off remove the beaker from the steam. Add 25 mils of normal sulphuric acid in 10-mil portions, warm the mixture slightly and then filter into a separator after each portion of the dilute acid is added, and finally wash with a little water. Then shake out the solution five times with 15-mil portions of chloroform, preserving the chloroformic extracts in another separator. Wash the latter with 10 mils of distilled water, discard the chloroform, and add the wash water to the acid liquid which was shaken out with the chloroform. Then add 10 mils of petroleum ether (boiling at 40°–60° C.) and thoroughly shake the separator, separate the acid liquid, and discard the solvent. Add a slight excess of ammonium hydroxide, cool the mixture, and then shake out the solution with 15 mils of petroleum ether of the boiling-point before specified and reserve the solvent solution in another separator. Shake twice again with the same quantity of solvent, then wash the combined petroleum ether solutions once with distilled water and filter into a small beaker, washing the separator and filter with 10 mils of petroleum ether. Evaporate the petroleum ether rapidly over a steam-bath, using a fan, and if cocain was present in the original material it will be found in the residue.

By this method it is possible to obtain the cocain in a very pure condition; in fact, it will often crystallize in a few hours, even though the amount present be very small. The identification tests are conducted as follows:

Dissolve the residue in petroleum ether and pour portions of the solvent into a beaker and a small evaporating dish, reserving the remainder for subsequent tests. After the solvent has evaporated dissolve the contents of the beaker in 5 mils of normal sulphuric acid, warming if necessary, and add potassium mercuric iodide test solution.

The formation of a precipitate indicates the presence of an alkaloid, but, of course, does not identify it as cocain; if no precipitate occurs further tests are unnecessary.

To identify the alkaloid treat the contents of the evaporating dish with 2 mils of concentrated nitric acid and evaporate the mixture to dryness over the steam-bath. When there is no further odor of nitric acid remove the dish, cool, and add 5 to 10 drops of N/5 alcoholic potash

solution, noting carefully the color and odor of the mixture while the dish is cool and then applying gentle heat and noting the odor again.

Minute traces of cocain will give off the odor of ethyl benzoate on treatment with nitric acid and alcoholic potash. The odor is very marked in its character and can be readily distinguished, though until one is familiar with it a parallel test should always be run, using pure cocain.

The color reaction is also of interest and will prove valuable in detecting the presence of other alkaloids. A purple color would indicate that atropin, strychnin, or yohimbin were present, though it is well known that a residue obtained by the above method from the coca leaf will in some instances also give a purple color. Tropacocain, benzoylecgonin, and aconitin will also give the ethyl benzoate test, but the possibility of the presence of the first two can be eliminated by a subsequent microscopic test, and from the fact that the benzoylecgonin is not removed from the aqueous solution to any great extent by petroleum ether. The latter fact is also true of aconitin, but the presence of this very poisonous alkaloid would be readily apparent when performing the physiological test.

The portions of the material which had been reserved should be tested physiologically. The petroleum ether is evaporated, a part of the cool residue is placed on the tongue and rubbed gently with the finger for about one minute, when, if cocain is present, a sensation of numbness gradually develops, the tongue and often the lips which have been touched by the finger will have a smooth, ivory-like feeling, and the effect will be apparent for some time. This is another test which should be performed in conjunction with one on a known sample, unless the analyst is perfectly familiar with the sens tion.

This residue may also be used or a microscopic test by removing a small portion, placing it on a microscope slide and noting, under the lens, the character of the crystals found with a drop or two of gold chloride solution. Cocain forms a definite crystalline compound with gold chloride, and the product obtained should be compared with that given by a solution of the pure alkaloid.

With a residue obta ned originally as described, these tests will substantiate the presence of cocain even though it occur in a minute quantity, and the four reactions can be applied to very small residues, although if it is desired the first mentioned with potassium-mercuric iodide may be omitted.

Another reaction for cocain which is very characteristic when considered in conjunction with the ethyl benzoate test is obtained by transferring some of the residue to a pressure flask, adding a few crystals of salicylic acid and about 15 mils of dilute hydrochloric acid, and heating the flask, stoppered, for about an hour and a half over the steam-bath.

On opening the flask the odor of wintergreen will be very marked if cocain was originally present. Tropacocain does not respond to this reaction, though it might indicate the presence of cinnamyl cocain and the truxillins; all of the latter, however, are precluded if the mixture gives the ethyl benzoate test.

Howard and Stephenson[1] describe the results of their researches in determining the characteristic microscopic forms of the crystals of a number of cocain salts, and the essential points of the work are summarized as follows:

Crystalline deposits have been obtained with each of the following eleven reagents, viz., palladous chloride, platinum chloride, gold chloride, picric acid, chromic acid and hydrochloric acid, potassium dichromate and hydrochloric acid, potassium permanganate, potassium chromate, sodium carbonate, ferric chloride, and potassium hydrate or sodium hydrate; noncrystalline deposits were obtained with chlorzinc iodid, picralonic acid, Mayer's reagent, phosphomolybdic acid, phosphotungstic acid, Kraut's reagent, Wagner's reagent, barium mercuric iodide, and potassium cyanide.

The following observations were noted concerning the various reactions with cocain in which crystals were produced:

Palladous Chloride —This is one of the most characteristic tests for cocain, though not quite so sensitive as gold chloride. The crystals vary in form greatly, according to the conditions of precipitation. There is at first formed, except in very dilute solutions (1 : 300 and up), an orange-colored amorphous-like or oily precipitate from which, on standing, crystalline forms of golden-brown color are produced. One of the most common forms is that obtained with a 1 : 100 dilution, when feathery crystals are formed which have a strong tendency to twin. With a solution of 1 : 20 a dense precipitate is thrown down, out of which hexagonal plates are at first formed and frequently followed later by sheaf-like clusters of fine-pointed acicular crystals. A dilution greater than 1 : 500 gives crystals only with difficulty, crystallization being induced by rubbing the slide with the glass stirring rod. The limit of the test is 0.2 μ gr.

Platinum Chloride.—With a 1 : 20 solution a dense white precipitate is formed and quickly followed by the production of very narrow feathery crystals—many times twinned so as to resemble a bird with outspread wings. Clusters of more than two are also abundant. If the reagents are mixed slowly the crystals are more like those of greater dilution. With a 1 : 100 dilution the feather type is much more prominent, the secondary branches being well developed into frost-like forms. With 1 : 1000 solutions either short thick crystals are formed or else plate crystals twinning

[1] U. S. Dept. Agri. Bull. 122, Bureau Chemistry, p. 99.

in a most characteristic manner are produced. The dilution limit is about 1 : 4000, and the limit in 1 : 1000 is 0.2 μ gr.

Gold Chloride.—This is the most sensitive reagent for cocain so far found. At 1 : 100 feathery frost-like crystals are produced, together with some nearly smooth star-like aggregates. At 1 : 1000 the form is much the same, but the branches usually bear a rough outline. Diamond plates are also produced. At 1 : 4000 a cross-like form predominates, the cross-bar being short. A few rosette crystals frequently are present. Crystals can be obtained in dilution up to 1 : 20,000, and the limit of the test for dilutions of about 1 : 300 is 0.033 μ gr.

Picric Acid.—This is a good reagent for dilutions up to 1 : 800, though the crystals produced are not very characteristic for this alkaloid. They are produced in spherical rosettes (or sheafs) of fine lemon-yellow acicular forms. The reaction takes place quickly, and no difficulty is experienced in producing them nearly to the limit of dilution. At 1 : 300 the limit is 0.2 μ gr.

Potassium Permanganate.—With cocain, solutions up to a dilution of 1 : 700 give purple-colored square plates, or aggregates of this form. Vigorous rubbing of the slide is often necessary to start the crystallization, which then proceeds readily. When they begin to crystallize spontaneously, the plates are sometimes deposited in spherical aggregates. The limit at 1 : 400 is 2 μ gr.

Chromic Acid and Hydrochloric Acid.—This test is made by adding a small drop of 5 per cent chromic acid solution to the test drop. A precipitate is formed which on stirring disappears (if too much has not been added). A small drop of strong hydrochloric acid is added, and a yellowish deposit is produced which, after rubbing of the slide, should in a few moments be transformed into loose spherical clusters of an acicular crystal. This test appears to be one of the most uncertain, because of the difficulty with which the crystallization is sometimes induced to being in dilutions greater than 1 : 60. A concentration of 1 : 1000 has produced positive results on standing several minutes. The limit appears to be for 1 : 100 about 3 μ gr.

Potassium Bichromate and Hydrochloric Acid.—This test gives the same form of crystals as the chromic acid and the test is conducted in a similar manner. The limit of dilution is about 1 : 1000 while at 1 : 100 the limit is 3 μ gr.

Ferric Chloride.—The crystals are spherical aggregates of rather coarse blade-like crystals with chisel-shaped ends. The limit of dilution is about 1 : 1000 and in a dilution of 1 : 100 the limit is 3 μ gr.

Potassium Hydrate, or Sodium Hydrate.—This produces a white amorphous precipitate which changes into crystals on standing or by rubbing the slide with a glass rod. The crystals are rod-like, frequently with more

or less chisel-like ends and a V-shaped recess extending backward into the crystal. There is a strong tendency to form coarse clusters up to about fifteen branches. In open drops tree-like forms are frequent. For each of these reagents dilutions up to 1 : 1000 give the reaction and the limit at 1 : 100 is 3 μ gr.

Sodium Carbonate.—This gives a precipitate with cocain like that produced by potassium hydrate, both in the amorphous and crystalline forms. Limit of dilution is 1 : 1000. In 1 : 100 solution the limit is 3 μ gr.

In order to determine the usefulness of some of the above tests when other alkaloids are present the palladous chloride test was made on test drops to which had been added solutions of one of the following alkaloids: codein sulphate, atropin sulphate, heroin, dionin, acoin powder, cinchonin sulphate, hydroxylamin hydrochloride, apomorphin hydrochlorate, narcotin, papaverin, brucin, narcein, morphin, thebain, gujasanol, orthoform (new), cinchonidin sulphate, quinidin sulphate, beta-eucain, holocain, caffein, quinin sulphate, strychnin, and tropacocain. In each case the crystals of the cocain compound were obtained and in the case of brucin, gujasanol, caffein, strychnin, and tropacocain, with which the palladous chloride regularly gives a crystalline precipitate, it was found that when cocain was also present the cocain product was given in addition to that for the other alkaloid, though occasionally with modified form.

QUANTITATIVE DETERMINATION OF ALKALOIDS IN COCA EXTRACTS AND SEPARATION OF COCAIN

The alkaloidal residue obtained in the assay of coca leaf or the extract made from this drug does not show the actual cocain content. This alkaloid may be present to the extent of 40–90 per cent.

From solutions containing extract of Coca, and where the Belladonna or Cinchona alkaloids are not present, the Coca alkaloids may be separated in the same way as they are from the extract obtained from the drug in the assay methods.

Caffein may be separated from cocain by taking advantage of the fact that the former can be removed by chloroform from solution acidulated with sulphuric acid.

The methods for determining the ether soluble alkaloids in Coca leaf have already been detailed.

In order to determine the actual cocain present in the alkaloidal residue obtained in the assay of Coca leaf or preparations containing this drug the following method of Garsed [1] may be used:

The crude alkaloids, after thoroughly drying over sulphuric acid, are weighed. Then dissolve in dilute sulphuric acid and add potassium per-

[1] Pharm. J., 1903, 784.

manganate solution. Re-extract the unoxidized alkaloid from ammoniacal solution with ether, evaporate the solvent, dry carefully and weigh. The loss in weight represents the amount of cinnamyl cocain.

Subject the residue to alkaline hydrolysis as follows: Use about 20 mils N/10 alcoholic potash to every 0.1 gram of residue. Add to the mixture 20 mils distilled water and heat for half an hour on the water-bath, using a reflux condenser. Any volatile ester formed is, at this dilution, rapidly hydrolyzed. Evaporate alcohol, dilute with water to about 10 mils, place in a separatory funnel and wash with ether.

Add a slight excess of normal acid and extract three times with ether. Separate and evaporate ether extracts at a temperature below the boiling-point of ether. Add distilled water until a dilution of 1 : 500 is obtained and temperature kept at 14° C. Under these conditions the truxillic acid remains undissolved. Filter and wash thoroughly with water at 14°. Determine the benzoic acid in the filtrate by shaking out with ether and then separating the ethereal solution, adding to it in a separatory funnel a known volume of N/10 or N/50 alkali, extracting thoroughly and titrating the excess of alkali with N/10 or N/50 acid. From the figures obtained the amount of benzoic acid and from that the amount of cocain can be calculated.

Wash out the dish used in separating the benzoic from the truxillic acid with a small quantity of hot 90 per cent alcohol, pour through filter holding the rest of truxillic acid. Titrate with N/10 alcoholic potash. The figure obtained gives the amount of truxillic acid and from this the amount of truxillin can be determined.

Factor for cocain 2.48.

Factor for truxillin 2.22.

Another procedure is as follows: Subject the crude alkaloids at once to alkaline hydrolysis. Evaporate the alcohol but not to dryness. Bring the products of hydrolysis into solution in water, acidulate and shake out with ether. Evaporate ether at a low temperature and treat the residue with water at 14°, diluting to 1 : 500. Filter and wash, leaving behind the truxillic acid, as before mentioned.

Shake out the filtrate and washings with ether. Separate the ether, add a known volume of standard alkali, shake out and finally titrate the excess of alkali with standard sulphuric acid. This figure obtained represents both the benzoic and cinnamic acids. Now add to the solution a slight excess of standard sulphuric acid. Add to this an excess of standard bromine solution. (Bromine in potassium bromide.) Allow to stand with occasional agitation. Finally add potassium iodid solution, which removes the excess of bromine, and titrate the liberated iodine with standard sodium thiosulphate. From the figures obtained the cinnamic acid present can be calculated and by referring to the titration figures obtained

with the mixed cinnamic and benzoic acids the amount of the latter may be determined.

The truxillic acid left on the filter may be determined as in the previous method.

Factor for cinnamyl cocain 2.22.

Cocain is so easily removed by ether or petroleum ether from a solution made alkaline with ammonia that a determination of this alkaloid in products where it occurs as the salt is attended with little difficulty. The chief concern is to be sure that it is separated from the other alkaloids which may be present, and secondly, that in the process of manipulation no decomposition occurs.

Atropin and quinin follow cocain closely in solubility and in making a determination of cocain in their presence resort must be had to other than solubility methods.

In presence of quinin, cocain may be determined by heating both alkaloids under pressure in the presence of a dilute mineral acid at the temperature of the steam-bath for four hours at least. The benzoic acid resulting from the hydrolysis of the cocain can then be removed by ether and determined by titration. From the results obtained the amount of cocain may be calculated. If it is desired to determine both alkaloids, the residue given by the ether extract from ammoniacal solution should be weighed after drying. Then the mixed alkaloids may be subjected to the acid treatment above mentioned and the cocain determined from the benzoic acid. The difference will be the amount of quinin.

In order to determine the amount of cocain in pharmaceutical preparations, caution must be observed in order that the alkaloid does not become decomposed during the manipulation.

If the product is a liquid a weighed or measured quantity should be taken. If alcohol is present evaporate (in neutral solution if possible) until it is driven off. Then dilute the solution, render slightly acid with dilute sulphuric acid 2 per cent and filter if necessary into a separatory funnel. Now shake out once or twice with ether, and if caffein is present make four extractions with chloroform. Then add ammonia until the solution is alkaline and shake out three times with petroleum or sulphuric ether. Combine the ether extracts, wash once with distilled water, and then filter the ether solution into a tared dish, carefully washing the filter paper and funnel. Dry at a low temperature and weigh. Then titrate the residue with N/50 standard acid and alkali.

If the residue is a mixture of coca alkaloids and it is desired to specify the actual amount of cocain the residue after weighing above should be treated according to Garsed's method.

If the analyst is working with pills or tablets, these products should be carefully ground, and a weighed portion throughly extracted with

alcohol. The alcoholic solution is then evaporated and the residue taken up with dilute sulphuric acid, filtered if necessary, into a separatory funnel and the above procedure followed.

When working with an ointment or other product containing grease, place a weighed amount in an Erlenmeyer flask and add ether. Add water and sufficient ammonia to render the solution alkaline. Rotate the flask for fifteen or twenty minutes and then transfer the mixture to a separatory funnel, using caution to prevent any loss. Run off the aqueous solution into another separatory funnel and shake it out twice more with ether. Combine all the ether extracts, shake out three times with 2 per cent sulphuric acid, collecting acid washings in a fresh separatory funnel. Make alkaline with ammonia, shake out three times with petroleum or sulphuric ether, filter into tared dish and weigh.

COCA LEAF

A systematic examination of the coca leaf has shown the presence of a small quantity of material volatile with steam to which the odor and flavor are partly due; from 2–5 per cent of wax; a little saponifiable fat; chlorophyll, from 5–10 per cent of a complex resin which contains a substance contributing to the odor of the drug; from 8–15 per cent of a tannin-like substance; an appreciable quantity of ecgonin; the salts of a phosphorus acid and unidentified organic acids amounting to about 10–20 per cent; complex carbohydrate-like substances; 8–10 per cent of proteins, cellulose, and allied substances.

The nitrogenous material in coca leaf is quite considerable, and a portion of it only is represented by the alkaloids and ecgonin.

The volatile material contains a little methyl salicylate.

The tannin-like substance appears to be characteristic of coca. It is difficult to obtain in a pure and unaltered condition, owing to its susceptibility to the action of reagents and heat. When first obtained it is readily soluble in alcohol and water, but it is easily converted to a form analogous to ellagic acid, which is insoluble in water. Its properties have been described, but as some authors have tested the soluble and others the insoluble form, the literature is confusing. Up to the present time the most important communication on cocatannic acid was made by C. J. H. Warden,[1] who worked with Indian-grown leaves. He describes a yellow amorphous body, almost insoluble in water, which he claims has the formula $C_{17}H_{22}O_{10}$. Investigation has since shown that the substance described was an anhydride or some transformation product of the tannin, and that probably it contained a small quantity of the tannin, which was the portion that Warden found soluble in water.

[1] Pharm. Journ. and Trans., 3d series, 1887–8, 985.

The separation of the tannin-like substance presents some difficulty, owing to the fact that it is readily decomposed or polymerized on heating and in contact with acids, and furthermore it is very hygroscopic. It can be partially removed from an acid aqueous liquid by means of ethyl acetate, and it is best removed from the leaves by first making a thorough extraction with anhydrous ether to dissolve coloring matter, fats, and waxes, and then percolating with 95 per cent alcohol. The alcohol dissolves the tannin and resinous constituents, and on concentrating, rendering anhydrous with sodium sulphate and precipitating by pouring into a large volume of chloroform, the tannin is obtained as a yellowish-brown precipitate, which can be filtered off and dried *in vacuo* over sulphuric acid.

As first obtained, this yellowish substance will be completely soluble in water, but on standing the insoluble form gradually develops. An aqueous solution gives a deep olive-green color with ferric chloride, and the same color and an olive-green precipitate with ferric acetate. It gives a yellow precipitate with bromin water, and a white precipitate with silver nitrate, the latter turning gray on standing, leaving the supernatant liquid colorless. With gelatin no precipitate is obtained, even in the presence of sodium chloride, but on adding sulphuric acid in the presence of gelatin a white precipitate is thrown out. Cinchonin sulphate produces a slight but definite precipitate. Potassium ferricyanide and ammonia give a deep brownish-yellow color with a reddish cast. Lead acetate gives an orange or reddish-yellow precipitate. Lime water produces a yellow color, but no precipitate. No observable reaction is obtained with starch, antipyrin, barium chloride, magnesia mixture, ammonium molybdate, alum, or borax. Reduction occurs with permanganate and to a slight extent with Fehling's solution.

Attempts to determine the character of the tannin have as yet yielded no information on which definite conclusions can be based.

SYNTHETIC ANESTHETICS

The advance of synthetic chemistry has resulted in the evolution of a number of artificial anesthetics, some of which have assumed considerable importance, and as they are often substituted for cocain they will be considered at this point.

Most of these substances have well-defined characteristics, they are offered in the pure state or in mixtures from which they can be removed by simple means, so that their identification should present no difficulty, and it is not likely that the analyst will encounter more than one individual at a time.

Beta eucain, holocain, eupthalmin, novocain, the orthoforms, stovain, chloretone, acoin, alypin, and anesthesin are being employed to a considerable extent.

Most of them are basic in character, dissolving readily in acids and removable from alkaline solutions by immiscible solvents.

These anesthetics fall into several different groups, the members of each group resembling each other to a greater or less extent.

Thus the eucains and eupthalmin are derivatives of gamma-oxymethyl piperidin; holocain and acoin may be considered derivatives of anilin antipyretics; the orthoforms, anesthesin and subcutin, are derivatives of benzoic acid; the derivatives of glycocollamido carbonic acid are represented by nirvanin; the derivatives of guaicol include brenzcain, guaisanol, and guaiacyl; alypin, novocain, and stovain from a fairly well-defined group; and chloretone is trichlor tertiary butyl alcohol.

THE EUCAINS

Alpha Eucain

The hydrochloride of benzoyl-*n*-methyl-tetramethyl-gammaoxy-piperidinecarboxylicmethyl ester.

It has almost entirely been displaced by beta eucain.

The free base is precipitated from its aqueous solutions by ammonia, alkali, and alkali carbonates; it forms a pasty mass which quickly becomes crystalline.

If 5 mils of a 1 per cent solution of alpha eucain is treated with 3 drops 5 per cent chromic acid a beautiful yellow precipitate appears immediately.

If 5 mils of a 1 per cent solution is treated with 30 mils 10 per cent potassium iodid solution, a milkiness appears and after a short time colorless plates of eucain hydrogeniodid form and separate.

Neither of these two reactions is given by cocain.

Beta Eucain $C_5H_7N(CH_3)_3(C_6H_5COO)\cdot HCl$

The hydrochloride of benzoyl-vinyl-diaceton-alkamin, or 2, 6, 6-trimethyl-4-benzoyl-piperidin.

The salt forms a crystalline powder soluble 1–25 in water at 15° C., more soluble in warm water. It melts at 268° C.

The free base is precipitated by ammonia, alkalies, and alkali carbonates, and is liquid at the ordinary room temperature

A solution of the salt gives precipitates with Mayer's reagent, iodin in potassium iodide, phosphomolybdic acid, phosphotungstic acid, potassium chromate, potassium bismuth iodide and picric acid. No precipitate occurs with mercuric chloride unless the solution is concentrated, and the precipitate is soluble in excess of the reagent. With chromic acid a precipitate is given in concentrated solution, it is amorphous and soon agglomerates and dissolves in strong hydrochloric acid. When a

1 per cent solution is treated with chlorine water a dense white turbidity occurs, differing from cocain which gives no precipitate.

A crystalline precipitate is thrown down by platinic chloride, which has a characteristic form under the microscope. The precipitate with gold chloride is amorphous.

When its acid solution is treated with ammonia a white precipitate is formed which is readily soluble in petroleum ether.

Parsons[1] has studied the reactions of the eucains with special reference to distinguishing them from cocain.

Potassium iodide (1 : 10) gives, in even moderately dilute solutions of α-eucain hydrochloride, a white silky and glistening precipitate. This precipitate has much the same appearance as the one obtained when stannous chloride is added to a cold dilute solution of mercuric chlorid. β-eucain and cocain give no reaction.

"Ammonia, even in dilute solution, precipitates the bases α- or β-eucain or cocain, but α-eucain is almost insoluble in excess. In 1 per cent solution the white precipitate is at once thrown down, and in the case of β-eucain or cocain dissolves immediately on addition of about their own volume of strong ammonia. α-eucain, so precipitated, can be diluted at least ten times with strong ammonia without solution. In stronger solutions the difference still exists, but is not so easily recognized. A 3 per cent solution of β-eucain or cocain requires about five times its own volume of ammonia to be dissolved, and stronger solutions much in proportion to the per cent present. In other words, a strong solution of ammonia will dissolve about $\frac{1}{2}$ of 1 per cent of the bases β-eucain or cocain, while it will dissolve but a very small fraction of a per cent of α-eucain. In dilute solutions this is a very characteristic reaction for α-eucain and strong solutions are, of course, very easily rendered dilute for the test.

Potassium dichromate, in strong solution, added drop by drop to a 0.5 per cent solution of α-eucain, begins to throw down a fine lemon-yellow precipitate after addition of 1 or 2 drops. The precipitate is then much increased by 1 or 2 drops of strong hydrochloric acid, and is then quite soluble, dissolving only after several times diluting the volume of the solution. With stronger solutions the precipitation takes place at once, the first drop giving a more and more permanent precipitate as the solution grows stronger. The precipitate is notably insoluble in either water or hydrochloric acid. More dilute solutions will show no precipitate or only after addition of hydrochloric acid. Cocain, 1 per cent, solution, is not precipitated by potassium dichromate, but the addition of 1 or 2 drops of concentrated hydrochloric acid throws down a yellow precipitate easily soluble in very slight excess of hydrochloric acid on dilu-

[1] American Journal of Pharmacy, 1902, p. 198, Jour. Amer. Chem. Soc., 1907, p. 885.

tion of the solution with water. Weaker solutions do not precipitate, while stronger solutions precipitate at once. The precipitate, however, is easily soluble as before. β-eucain acts like cocain. The precipitate in all cases is lemon-yellow. The α-eucain precipitate is quite crystalline. All three may throw down a small amount of a yellow colloidal precipitate which sticks to the side of the test-tube and dissolves but slowly, although this in nowise interferes with the test, and does not take place if reagents are added slowly. While this test depends upon the very much greater insolubility of the α-eucain salt, the non-precipitation in dilute solutions of a certain strength until after the addition of hydrochloric acid is quite characteristic for all. The correct strength is about 0.5 per cent solution of α-eucain and about 1 per cent for β-eucain and cocain. In the case of cocain and β-eucain, the test may be conveniently applied by precipitating a stronger solution than 1 per cent with potassium dichromate solution, diluting carefully with water until precipitate just dissolves. On addition of a drop of concentrated hydrochloric acid the precipitate will at once reform. This cannot be done with α-eucain, for precipitate once formed it is difficult to get it to dissolve at all.

Chromic acid (1 : 20) acts similarly to the dichromate.

If a small amount of cocain hydrochloride be rubbed up with dry mercurous chloride (calomel) and then moistened with alcohol, it rapidly turns to a grayish black. α-eucain hydrochloride becomes slowly a dark gray. β-eucain hydrochloride is not affected.

Platinic chloride throws down slowly a yellow crystalline precipitate from a 1 per cent solution of cocain hydrochloride, which is insoluble in hydrochloric acid. α- and β-eucain hydrochloride in 1 per cent solution are not altered. In stronger solutions all three hydrochlorides are immediately precipitated by platinic chloride, but the cocain precipitate is not soluble in hydrochloric acid, while the precipitates by either eucain are at once dissolved.

Cocain solutions almost always cause mydriasis; β-eucain does not dilate the pupil.

The lactate of β-eucain is a white non-hygroscopic powder melting at 152–155° C. and readily soluble in water and alcohol. The base is precipitated by ammonia and alkalies and responds to the usual characteristic reactions.

If 1 gram of β-eucain lactate is warmed with a few drops of dilute sulphuric acid and 1 mil of potassium bichromate (1 : 10) the odor of acetaldehyde is evolved.

Eupthalmin Hydrochloride

The hydrochloride of phenyl-glycolyl-*n*-Methyl-beta-vinyl-diaceton-alkamin.

It is the mandelic acid derivative of beta eucain, and possesses marked mydriatic properties. It is not an anesthetic.

The salt forms a colorless crystalline powder. Its solution gives precipitates with Mayer's reagent and with iodine in potassium iodide, phosphomolybdic and phosphotungstic acids. No precipitate occurs with potassium chromate, nor with platinic chloride or chlorine water.

When evaporated with nitric acid a yellow residue is left which on treatment with alcoholic potash gives off an odor of benzaldehyde and red oily drops appear.

On treating with a solution of molybdic acid in sulphuric acid no color appears at first, but on standing the outer rim becomes blue.

Holocain Hydrochloride

Holocain. Para-diethoxy-ethenyl-diphenylamidin.

$$CH_3C=(NC_6H_4OC_2H_5)NHC_6H_4OC_2H_5$$

The base is a condensation product of para-phenetidin and acetphenetidin and forms white crystals melting 121°; insoluble in water.

The hydrochloride is soluble in water and alcohol.

An acid solution of holocain gives a white precipitate with ammonia which is slightly soluble in petroleum ether but readily soluble in ether.

Precipitates are produced by the ordinary alkaloidal reagents. An aqueous solution acidified with hydrochloric acid gives a white precipitate and with mercuric chloride, and with calcium hypochlorite a violet precipitate is obtained, soluble in ether, and imparting to it a red color.

When evaporated with nitric acid the base leaves a yellow residue which turns red on the addition of alcoholic potash and gives off a disagreeable odor.

Acoin

Di-para-anisyl-monophenetyl-guanidin-hydrochloride.

$$(CH_3OC_6H_4NH)_2CNC_6H_4OC_2H_5+HCl$$

Acoin is a white crystalline powder—melting-point 176°, soluble in water.

Its solutions are precipitated by the ordinary alkaloidal reagents and with bromine water a dirty-yellow curdy precipitate forms which turns to purple on adding ammonia dissolved in chloroform.

Immediate reduction takes place with permanganate.

The base is somewhat soluble in petroleum ether, and readily soluble in ether. It gives a deep red color with nitric acid and on treating the evaporated product with alcoholic potash an agreeable odor is given off.

The Orthoforms

Orthoform.—

Para-amido-meta-oxybenzoic-methyl-ester.

$$C_6H_3(COOCH_3)NH_2OH\ 1\text{–}4\text{–}3$$

It is a white, odorless, tasteless, crystalline powder; slightly soluble in water, readily soluble in alcohol, and melting 118–120° C.

Its solution in acetic acid gives a green color with PbO_2.

Orthoform " New ".—

Meta-amido-para-oxybenzoic-methyl-ester,

$$C_6H_3(COOCH_3)NH_2OH,\ 1\text{–}3\text{–}4.$$

Fine white powder, difficultly soluble in water, readily soluble in 5 to 6 parts of alcohol, soluble in ether 1–50, and alkalies.

It occurs in two modifications, sometimes crystallizing out of chloroform in quadratic plates melting at 110–112° C. As a general thing, however, it crystallizes in shining needles melting at 142°. The lower melting modification is transformed to the higher on fusion.

Its solutions are neutral. A cold aqueous solution is colored red by ferric chloride, and on heating the red is changed to green. On boiling the aqueous solution, orthoform is decomposed into methyl alcohol and paraoxybenzoic acid.

If 0.1 gram is dissolved in 2 mils of water with help of a little dilute sulphuric acid, and a few drops of sodium nitrite solution added, the solution becomes yellowish red and a yellow precipitate comes down which becomes intensely red in contact with the air.

With concentrated nitric acid a blue color changing to red occurs. No odor develops on the subsequent addition of alcoholic potash. The other orthoform gives a green color with nitric acid.

It gives precipitates with phospho-molybdic and phosphotungstic acids. With bromine water a yellowish green precipitate is obtained differing from most of the other synthetic anesthetics which give a white or a yellowish precipitate. On subsequently adding ammonia the green precipitate gives way to a dark-red solution. It does not give precipitates with either Mayer's or Wagner's reagents.

It is practically insoluble in petroleum ether, very slightly soluble in chloroform, more readily in ether.

The Orthoforms combine with chloral to form tasteless products of great hypnotic action. They are difficultly soluble in water but readily so in alcohol and ether and on warming with mineral acids are broken up, chloral being liberated.

Anaesthesin

Ethyl ester of paramido benzoic acid.

$$C_6H_4NH_2COOC_2H_5$$

It forms a white odorless, tasteless powder, melting 89–91° C. It is sparingly soluble in cold water, readily soluble in hot water and in organic solvents, except petroleum ether, in which it dissolves but sparingly. It dissolves readily in fixed oils and fats. It is removed by solvents from acid solution.

0.1 gram anesthesin treated with 100 mils of water and a little hydrochloric acid followed by a few drops of sodium nitrite solution and an equal quantity of beta-naphthol solution results in the production of an intense cherry red color changing to orange with acids.

On boiling with alkalies it is decomposed into paramido-benzoic acid and ethyl alcohol.

It gives precipitates with the ordinary alkaloidal reagents, except Mayer's reagent and tannic acid. No precipitate is given with potassium chromate until the solution is acidified, when a brown deposit takes place with reduction. Immediate reduction occurs with potassium permanganate. A dark greenish-black residue is left on evaporation with nitric acid and no odor is given off with alcoholic potash.

Propaesin

Propylester of paramido benzoic acid.

$$C_6H_4NH_2COOC_3H_7$$

This substance occurs as a white bulky crystalline powder, neutral to litmus and having a melting temperature 74–76°. It is slightly soluble in water, and with difficulty in dilute sulphuric acid, unless the liquid is warmed, but it is readily soluble in alcohol, chloroform, and ether.

An acid solution of propaesin does not give a precipitate with Mayer's reagent but other usual alkaloidal reagents, Wagner's, phosphomolybdic acid, phosphotungstic acid give immediate precipitates. With potassium chromate no reaction occurs, but after adding an equal volume of concentrated hydrochloric acid, the mixture darkens and a dirty brown precipitate comes out. The same reaction occurs in the case of 5 per cent chromic acid and hydrochloric acid. Potassium permanganate, when in dilute solution, is at first decolorized when added to an acid solution of propaesin; but as soon as an excess is present the permanganate is reduced. Bromin water gives a white precipitate and no change occurs when ammonia is subsequently added. An aqueous solution of its hydrochloride gives precipitates with platinic chloride and with palladium chloride.

No characteristic color reactions occur with oxidizing agents, nor with mineral acids. Ammonium vanadate gives a purple color soon changing to brown and gradually fading into gray, the best results apparently occurring when the propaesin is in considerable excess. When treated with nitric acid and evaporated over the steam-bath, the residue gives no characteristic odor when alcoholic potash is added.

Propaesin is removed from its acid solutions by ether and by chloroform, and from its alkaline solutions petroleum ether will separate it readily, though this solvent removes it but slightly from acid solutions.

When heated with a solution of potassium hydroxide it melts and forms an oily layer. If this mixture is boiled, propyl alcohol is evolved which may be recognized by its odor, and the alkaline liquid will contain paramido benzoic acid. The latter may be separated by neutralizing with mineral acid.

Subcutin

Para-phenolsulphonic acid-ethyl ester of para-amidobenzoic acid.

$$C_6H_4(COOC_2H_5)NH_2SO_3HC_6H_4OH$$

The paraphenol sulphonic acid derivative of anesthesin.

It is a white crystalline powder melting-point 195.6°. This product is not readily soluble in cold water, but on warming the liquid it dissolves readily, the odor of ethyl benzoate being very marked. The aqueous solution obtained either in the cold or on warming is acid to litmus. It is readily soluble in ether, but does not dissolve to any great extent in chloroform and petroleum.

It is completely removed from a solution acidulated with sulphuric acid by ether and partly by petroleum ether. From ammoniacal solutions it is much less readily given up to solvents.

An acid solution gives no precipitate with Mayer's reagent, but it reacts at once with iodine solution, the precipitate soon separating out in oily drops. Precipitates are given by picric acid, palladium chloride, phosphotungstic and phosphomolybdic acids and bromin water. Tannic acid gives no precipitate. Chromic acid solution produces a turbidity which is not changed on the addition of hydrochloric acid, and on standing a brown precipitate gradually settles. Potassium chromate gives no precipitate but on adding hydrochloric acid a deep red to brown color appears and a brown precipitate is found. Immediate reduction occurs with potassium permanganate. Ferric chloride solution in small amount produces a brownish purple but the color changes to a yellowish on adding more of the reagent. This reaction is not given by anesthesin. Formaldehyde sulphuric acid acting directly on subcutin gives no color at first, but a salmon shade soon develops, which gradually darkens to red then becomes

brownish red and finally brown. Ammonium vanadate produces immediately a beautiful green changing at once to blue and disappearing in a moment. Neither of these reactions is given by anesthesin. With sulphuric acid and bichromate a green color appears at once. On evaporating to dryness with nitric acid a brownish-yellow residue is left. Alcoholic potash becomes blood red when added to this product and an agreeable odor differing somewhat from ethyl-benzoate is given off.

Cycloform. Isobutyl paramidobenzoate

$$C_6H_4(NH_2)COOCH_2CH(CH_3)CH_3$$

Cycloform is a white crystalline substance, melting 65°, slightly soluble in water, but dissolving readily in alcohol, ether, and benzol. When heated with concentrated sodium hydroxide it evolves isobutyl alcohol, recognized by its odor.

Nirvanin

The hydrochloride of diethyl glycocoll-*p*-amido-*o*-oxybenzoic acid-methyl ester.

$$HCl(C_2H_5)_2N\ CH_2CONHC_6H_3(OH)COOCH_3$$

It forms white prisms melting at 185° C., soluble in water and alcohol. The base is precipitated by sodium hydrate or ammonia as a white solid, soluble, in excess, but in the case of ammonia a precipitate reappears on warming.

Its solution gives precipitates with all the ordinary alkaloidal reagents, and a violet color with ferric chloride.

On evaporating with nitric acid a red-colored residue is left which gives no characteristic odor on the addition of alcoholic potash.

Alypin

The hydrochloride of benzoyl-tetramethyl-diamino-ethyl isopropyl alcohol.

$$(CH_3)_2NCH_2C(C_2H_5)(C_6H_5OO)(CH_2N(CH_3)_2)HCl$$

Alypin is a white crystalline powder melting 169°. It forms a neutral solution in water which is not rendered turbid by sodium bicarbonate. Its solutions give precipitates with Mayer's and Wagner's reagents, with phosphomolybdic and phosphotungstic acids and with bromin water, but no precipitate occurs with potassium chromate. Potassium bichromate produces a yellow crystalline precipitate soluble in hydrochloric acid. Potassium permanganate produces a violet crystalline precipitate which turns brown on standing.

On the addition of alcoholic potash to a residue obtained by the evaporation of alypin with nitric acid, a disagreeable odor is given off.

The free base is a colorless, strongly alkaline oil which is somewhat soluble in water.

When warmed with sulphuric acid at the temperature of the water-bath, and then diluted with a little water, the odor of ethyl benzoate is evolved.

Stovain

Ethyl-dimethyl-amino-pentanol-benzoyl-hydrochloride.

$$C_6H_5COO(CH_3)CC_2H_5CH_2N(CH_3)_2HCl$$

Stovain forms small glassy plates, melting 175° C., soluble in water, alcohol, and acetic ether, but almost insoluble in ether. The free base is precipitated by alkalies, and may be removed from solution by immiscible solvents, petroleum ether dissolving it readily.

It is not precipitated by potassium iodide, but is thrown down by all the other alkaloidal reagents. It is precipitated by sodium bicarbonate and in this respect and in its action with potassium iodide it differs from alypin.

The residue obtained on evaporation with nitric acid gives off an odor of ethyl benzoate and isonitrile when treated with alcoholic potash.

0.1 gram of stovain treated with 5 mils sulphuric acid and heated for five minutes at 100° C. gives off the odor of ethyl benzoate on adding 5 mils water.

Novocain

The hydrochloride of para-amino-benzoyl-diethyl-amino ethanol.

$$C_6H_4NH_2(1)COOC_2H_4N(C_2H_5)_2(4)HCl$$

The hydrochloride is a crystalline salt soluble in water 1–1 and in alcohol 1–30. Melting-point 150-155°.

Caustic alkalies and alkali carbonates precipitate the base as an oily mass which crystallizes when cool. Sodium bicarbonate does not precipitate the base. From ether the base crystallizes in the anhydrous state, melting at 58–60°, while from alcohol it crystallizes with $2H_2O$, melting at 51°.

It gives precipitates with alkaloidal reagents and is soluble in sulphuric and hydrochloric acids without color.

0.1 gram of novocain in 5 mils water treated with 2 drops hydrochloric acid and 2 drops sodium nitrite solution, gives a scarlet red precipitate when added to a solution of beta naphthol.

On evaporating with nitric acid a yellowish red residue is left which

on treatment with alcoholic potash becomes red and gives off the odor of isonitrile.

Potassium chromate gives no precipitate. On adding hydrochloric acid reduction to a green color occurs which becomes red on standing.

Novocain when mixed with mercurous chloride and moistened with alcohol turns dark similarly to cocain.

If 0.5 gram of novocain in 2 mils water be treated with potassium bichromate solution drop by drop a precipitate is formed which dissolves on shaking.

Chloretone

Trichlor-tertiary-butyl-alcohol.

$$(CH_3)_2COHCCl_3$$

Chloretone occurs in snow-white crystals having a camphoraceous odor and taste. It is volatile with steam. It is soluble in chloroform, acetone, alcohol, ether, petroleum ether, glacial acetic acid, glycerin, fixed and volatile oils, also in warm water to the extent of 1 per cent, but on cooling a portion crystallizes out, the cold saturated solution containing 0.8 per cent. It possesses a peculiar property of sliding and rotating about on the surface of water.

When applied to the tongue it causes first a slight peppery sensation, and then a numbness, the latter, however, being much less pronounced than that caused by cocain and unaccompanied by the slippery feeling.

Chloretone of the formula $(CH_3)_2COHCCl_3$ has a melting-point of 97° C. It forms solid solutions with water, these products having melting-points down to 75°, depending on the amount of water present, and it is in some of these latter forms that it occurs on the market.

Its solution in acid does not give precipitates with the ordinary alkaloidal reagents.

It is soluble with decomposition in strong sulphuric acid.

With cold dilute potassium hydrate solution alpha-chlorisobutyric acid results and with concentrated potash, acetone, chloroform, and methyl acrylic acid. It is soluble in dilute ammonia, from which solution it may be removed by means of immiscible solvents.

Deniges [1] describes the following qualitative reactions for chloretone and also gives a method for its quantitative determination:

If 5 mils of a 5 per cent alcoholic solution of chloretone be boiled with 1–2 mils of solution of sodium hydroxide and allowed to cool, the clear solution produced becomes turbid on addition of mercuric sulphate; or, if instead of mercuric sulphate a few drops of fresh sodium nitro-

[1] Rep. de Pharm., 1905, No. 11.

prusside are added, followed by acetic acid in slight excess, the well-known carmine color of Legal's acetone reaction is developed. Ammoniacal silver nitrate is decomposed by solution of chloretone in the cold; Fehling's solution is reduced by it on boiling. The quantitative determination by titration is effected by adding to 10 mils of a 1 per cent solution of chloretone, in diluted alcohol, 1–2 mils of solution of sodium hydroxide, free from chlorine, and 10 mils of alcohol, and heating the mixture to boiling. After cooling, 1–2 mils of nitric acid (1.39) are added, the liquid is adjusted with water to 100 mils and the sodium chloride formed is titrated in the usual manner with silver nitrate, using potassium chromate as indicator and calcium carbonate to render the liquid milky. One mol. of chloretone forms 3 mols. of sodium chloride.

Chloretone should always be looked for in remedies designed to relieve seasickness.

Guaiasanol. "Gujasanol"

Diethylglycocoll guaiacol hydrochloride.

$$C_6H_4(OCH_3)OCOCH_2N(C_2H_5)_2HCl$$

Gujasanol forms white prismatic crystals, melting 183–184° C., readily soluble in water, and the odor of guaiacol is apparent.

Mayer's reagent gives a yellowish white precipitate and Wagner's throws out a brown precipitate which soon becomes oily and sticks to the sides of the container. It gives a white precipitate with ammonia which is readily soluble in petroleum ether and remains a colorless oily liquid on evaporating the solvent.

Brenzcain

Guaiacol benzyl ester.

Pyrocatechin methyl benzyl ester.

$$C_6H_4OCH_3OCH_2C_6H_5$$

Brenzcain forms colorless crystals melting 62°, soluble in alcohol, ether, and oils, but insoluble in water. On warming with hydrochloric acid guaiacol results and with potassium permanganate and sulphuric acid benzaldehyde is formed.

Guaiacyl

Calcium ortho guaiacol sulphonate.

$$(C_6H_3(OH)(OCH_3)SO_3)_2Ca$$

Gaiacyl is a grayish-brown powder readily soluble in water and alcohol. Its aqueous solution is violet red.

CHAPTER VI

ALKALOIDS DERIVED FROM QUINOLIN

THE CINCHONA ALKALOIDS AND THEIR DERIVATIVES

CINCHONA bark and certain of the alkaloids contained therein, have an extended and important use in medicine. The drug itself, depending on the variety, may contain a number of different bases, and while the list is extensive numerically, the actual number with which the drug analyst will be concerned is small, being limited, except in rare instances, to four or perhaps five individuals, quinin, quinidin, cinchonin, cinchonidin, and cuprein. Pictet mentions twenty-one alkaloids in his list; Chick, in the new edition of Allen, gives thirty-one and later mentions homoquinin, which is described by Pictet in his original list, so the number may be left at thirty-two. Pictet divides the bases into six main groups according to their composition and according to the nature of the decomposition products which are produced by the action of mineral acids. Each of the first three groups contains a subgroup which differs from the main group only in possessing a slightly greater amount of hydrogen. Chick classifies the alkaloids in five groups as follows:

1. Cinchonin Class.
   - Paricin, $C_{16}H_{18}ON_2$
   - Cinchotin or Hydrocinchonin
   - Cinchamidin or Hydrocinchonidin } $C_{19}H_{24}ON_2$
   - Cinchonamin
   - Cinchonin
   - Cinchonidin
   - Homocinchonidin } $C_{19}H_{22}ON_2$
   - Cinchonicin
   - Paytin
   - Paytamin } $C_{21}H_{24}ON_2$
2. Quinamin Class.
   - Quinamin
   - Conquinamin } $C_{19}H_{24}O_2N_2$
   - Javanin
   - Cuprein, $C_{19}H_{22}O_2N_2$

3. Quinin Class.

Hydroquinin Hydroquinidin	$C_{20}H_{26}O_2N_2$
Quinin Quinidin Quinicin	$C_{20}H_{24}N_2O_2$

4. Cusconin Class.

Chairamin Conchairamin Chairamidin Conchairamidin Concusconin Aricin Cusconin Cusconidin	$C_{22}H_{26}O_4N_2$

5. Anhydro bases.

Dicinchonicin
Diquinicin
Homoquinin

In addition to these bases there have been reported a number of acid and neutral bodies including quinic, quinovic, caffeic, oxalic, and certain tannic acids, quinovine, quinia red, quinovic red, cinchocerotine, cinchol, cupreol, cholesterol, etc.

CINCHONA BARKS

The drugs containing these alkaloids are obtained from several trees belonging to the genera Cinchona and Remijia (family of the Rubiaceæ). Many species of Cinchona have been described, but those yielding bark of any practical importance are limited. Of the varieties of commercial importance may be mentioned pale, crown or loxa bark from Cinchona officinalis; yellow Peruvian or Calisaya bark from C. calisaya and hybrids; red bark from C. rubra and C. succirubra and its hybrids, and containing a high percentage of cinchonidin; pitayo bark from C. Patayensis; Columbian or Carthagina bark from C. lanceolata, C. lancifolia, C. cordifolia, etc.; Ledger bark from C. Ledgeriana, very rich in quinin; and cuprea bark from Remijia pedunculata. The value of a bark depends on its alkaloidal content and this is extremely variable, barks having as high a content as 15 per cent have been reported and from this it runs down to a fraction of a per cent. Under the present system of cultivation the trees are not destroyed when the bark is gathered, a part only is removed, the remainder being left intact and the stem is then covered with moss under ch new bark forms rapidly. Quinin, cinchonin, and cinchonidin are

the bases most frequently found, quinidin is less common and is never in large amount

Cinchona and its alkaloids probably enter into a greater number of combinations and have a wider field of application than any other drugs used in medicine. Their properties are tonic, febrifugal, and antiperiodic, and hence they are recommended in malarial troubles and in convalescence. The classes of pharmaceuticals containing them include a great variety of pills, tablets, elixirs, wines, syrups, capsules, and bitters.

First taking up cinchona extract we find that this product is used in a plain elixir of calisaya; in combination with bismuth and ammonium citrate, with pyrophosphate, with strychnin and pepsin, either altogether or with one or more; with beef extract and iron oxychloride in the beef, iron, and wine products; with malt extract; and in various alcoholic products known as bitters such as Dubonnet, Quinquina, Ferro China Bisleri, and Quinin whisky types.

Quinin sulphate occurs in pill and tablet formulæ and in elixirs and bitter tonics combined with iron pyrophosphate and strychnin sulphate. Among the pills and tablets may be mentioned combinations of quinin sulphate with strychnin, reduced iron, and arsenous acid used in malarial conditions in which will be found at times aloes, Podophyllum resin and Gelsemium extract; iron and quinin citrate; iron, quinin, and strychnin citrate; quinin sulphate, arsenous acid, strychnin, aconite, and morphin for neuralgia; phosphorus, iron, either reduced or as ferrous carbonate, and quinin, with and without strychnin and sometimes with Digitalis and ipecac; quinin, arsenous acid, gentian, and atropin sulphate; quinin sulphate and Capsicum or oleoresin black pepper; iron, quinin, and zinc valerianates, sometimes with gold and sodium chloride and sumbul root; Warburg tincture containing quinin sulphate, rhubarb, angelica seed, elecampane, saffron, fennel, gentian, zedoary root, cubeb, myrrh, white agaric, camphor, with or without aloes; bronchitis tablets of belladonna, ipecac, opium and quinin sulphate; coryza tablets of camphor, quinin, morphin, and atropin sulphate; or of similar composition with ammonium chloride and no atropin; rhinitis tablets of camphor, belladonna, and quinin sulphate; acetanilid and quinin sulphate; acetanilid, caffein, sodium bicarbonate, sodium bromide, and quinin sulphate; ergot, Digitalis, and quinin sulphate; hypophosphites compound containing the hypophosphites of quinin, calcium, iron, sodium, potassium, manganese, and strychnin, sometimes with guaiacol; the same bases are also presented as phosphates; rheumatic tablets composed of quinin sulphate, extracts of Colchicum, colocynth, Hyoscyamus, opium, and mercury; cold tablets composed of quinin hydrobromide, aloin, Capsicum, calomel, aconite, ipecac, and opium, sometimes with cascara; inspissated oxgall, pancreatin, colocynth, Nux Vomica, Taraxacum and quinin sulphate; and quinin sulphate

or bisulphate alone in tablets and capsules of various strengths. Quinin and urea hydrochlorate are used in hypodermatic tablets. The elixir formulæ often include pepsin and bismuth and ammonium citrate and the phosphate syrups will contain the phosphates of the alkaline earth and alkali bases.

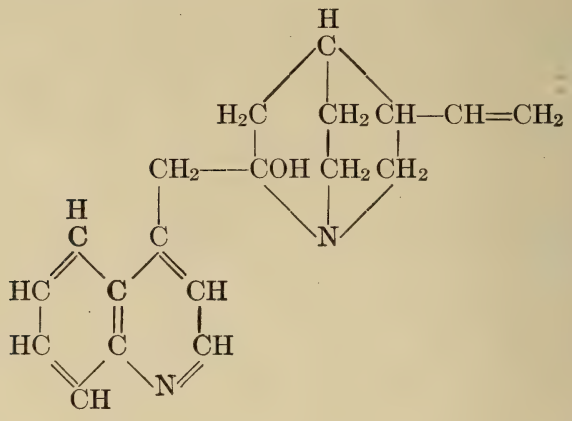
Quinidin will be found substituted for quinin and it is well to look for the former in all products which especially claim to be free from quinin.

Cinchonidin sulphate is combined with iron, arsenic, and strychnin in tablets and sometimes replaces quinin in the other formulas mentioned. It has been sold in an aphrodisiac compound mixed with Coca, phosphorus, Nux Vomica and bromides. It will be found in tonic pills with Xanthoxylum, dogwood and Capsicum, and is also marketed alone as is also cinchonidin salicylate.

Cinchonin sulphate has the same remedial properties as quinin sulphate and may be met with at any time, though its use is much limited compared to quinin.

Cinchonin

This alkaloid differs from quinin in lacking a methoxyl group, the constitutional formula accredited to it at present being



It is easily crystallized and melts from 250–265°, depending on its purity, and may be distilled unchanged in a current of hydrogen, ammonia, or *in vacuo*. It is somewhat soluble in boiling water, but almost insoluble in cold water, somewhat soluble in chloroform, benzol, amyl alcohol, and alcohol, and difficultly soluble in ether, especially when the solution and solvent are cold. It is a fairly strong diacid and bitertiary base, and both the alkaloid and its salts are dextrorotatory.

Cinchonin yields several isomers when acted upon by different chemical reagents. Among these may be mentioned cinchonidin, its stereoisomer,

which also occurs naturally, and cinchonicin, obtained by heating the alkaloid with very dilute sulphuric acid to 130° C.

The double bond in the side chain facilitates the addition of chlorine and bromine, giving in the cold, addition products. The dichloride and dibromide are crystalline, somewhat unstable, and behave as diacid bases. It also gives monobenzoyl, and monoacetyl derivatives due to the hydroxyl group.

The acid solutions of cinchonin are not fluorescent and the alkaloid does not give the thalleoquin test, thereby differing from quinin; it gives no well-defined characteristic color tests, but is precipitated by all of the ordinary alkaloidal precipitants including Mayer's and Wagner's reagents, phosphomolybdic and phosphotungstic acids, tannin, bromin water, gold chloride, platinic chloride, mercuric chloride, picric acid, potassium bismuthic iodide, and sodium carbonate; with potassium ferrocyanide it gives a precipitate soluble in excess; it is not precipitated by potassium iodide. It differs from its isomer cinchonidin, by not precipitating with Rochelle salts.

Cinchonin picrate melts 193–194° C.

Cinchonin forms a well-defined sulphate, containing two molecules of water, which become anhydrous at 100° C. This salt is much more readily soluble in water than is quinin sulphate, the saturated solution being about 2 per cent. The anhydrous salt is soluble in 60 parts of cold and in 22 parts of boiling chloroform which distinguishes it from the sulphates of cinchonidin and quinin.

Cinchonin hydrochloride contains two molecules of water and is readily soluble in water and alcohol, and somewhat in ether and chloroform.

Cinchonin iodosulphate is used as an antiseptic and is sometimes sold under the name "Antiseptol."

Ordinary commercial cinchonin contains considerable hydrocinchonin (cinchotin) often as much as 20 per cent, which renders the salts considerably more soluble than if chemically pure. Thus 1 part of pure cinchonin sulphate is soluble in 72 parts of water at 12° C., while the ordinary commercial salt requires but 64 parts, 1 part of pure hydrocinchonin dissolves in 37 parts of water.

Cinchonin is readily converted into isomeric substances. On heating with acetic acid it gives rise to cinchotoxin, a highly poisonous base. Pure cinchotoxin, when heated, first softens and then melts at 58–59° C. It is readily soluble in alcohol, acetone, chloroform, and benzene. In hot petroleum spirit it is less soluble, and separates on cooling in oily drops, which crystallize after some time. In contact with water it gradually becomes fluid, and a small portion passes into solution. This solution is precipitated and rendered turbid by addition of an excess of alkali. Cinchotoxin yields a series of crystalline salts, and forms a hydrozone

and several nitroso derivatives. The methyl derivative of cinchotoxin appears to be identical in all respects, chemical and physical—excepting some trifling differences in crystalline form, which require further investigation—with methyl-cinchonin. This similarity extends to their respective derivatives. On the other hand, cinchotoxin itself is absolutely indistinguishable—again excepting very slight disparities in the form of the respective crystals—from cinchonicin. The study of this compound and its derivatives went a long way to establish the constitution of cinchonin.

Cinchonin subjected to the action of sulphuric and hydrochloric acids under various conditions has yielded no less than 10 isomerides of the base, $C_{19}H_{22}N_2O$, namely α and β-isocinchonin, apoisocinchonin, apocinchonin, isoapocinchonin, diapocinchonin, dicinchonin, homocinchonin, pseudocinchonin, and cinchonicin.

The experiments described show how easily one base may be converted into another, and that such a change may actually occur during the process of the extraction of a base from the plant, or during the purification.

Cinchotenin

Cinchotenin is obtained by the oxidation of cinchonin with potassium permanganate with the formation of formic acid. The following equation represents the change:

$$C_{19}H_{22}N_2O+O_3=C_{18}H_{20}N_2O_3+H\cdot COOH$$

The reaction is general for the cinchona alkaloids, and has been investigated in the cases of cinchonidin, quinin, and quinidin.

Cinchonidin

Cinchonidin, the stereoisomer of cinchonin, accompanies quinin in all the cinchona barks, and in the extraction of the alkaloids it separates chiefly with quinidin. It is especially characteristic of the bark of C. succirubra. It crystallizes from alcohol in prisms melting 202–203°, very sightly soluble in water, somewhat soluble in ether and readily soluble in alcohol, chloroform, and amyl alcohol. Both the alkaloid and its salts are lævorotatory.

Cinchonidin gives precipitates with all of the usual alkaloidal reagents and is distinguished from cinchonin by yielding insoluble compounds with potassium iodide and with Rochelle salt. The precipitate obtained with potassium chromate is much more soluble than that given with cinchonin. Its acid solution is not fluorescent and it gives no thalleoquin test. The "Herapathite" test described under quinin yields microscopic needles without metallic luster. The picrate darkens at 200° and melts at 208–209° with decomposition.

Cinchonidin forms several well-defined salts, of which the sulphate is probably the one most universally met with in chemical work. The sulphate crystallizes with varying amounts of water, depending on the concentration and nature of the solvent; hot concentrated aqueous solutions yield a compound with three molecules of water, this being the salt official in the U. S. Pharmacopœia. The crystals lose their water when heated to 100° C. The anhydrous sulphate is almost insoluble in absolute chloroform, being similar to anhydrous quinin sulphate in this respect, and differing markedly from the sulphates of cinchonin and quinidin which go into solution readily.

In all of its reactions affecting its structure cinchonidin acts the same as cinchonin, most of their transformation and decomposition products being identical.

Cinchotin

This alkaloid, also called hydrocinchonin, contains two more hydrogen atoms than cinchonin and is found in crude cinchonin especially from the bark of Remejia purdieana. It may be isolated by treatment with permanganate which destroys the cinchonin more rapidly than the cinchotin is oxidized. It is dextrorotatory, melts at 286° (268° Mulliken), sparingly soluble in ether and forms addition products with hydrochloric and hydriodic acids. It forms a compound with methyl iodide which separates from methyl alcohol in pale yellow crystals melting 234–235°.

Cinchamidin

This alkaloid, also called hydrocinchonidin, is isomeric with cinchotin, melts at 230°, is lævorotatory, and resembles the latter in its general properties. It dissolves with difficulty in ether and is almost insoluble in chloroform even when hot. Its solutions in dilute mineral acids are fluorescent.

Cinchonamin

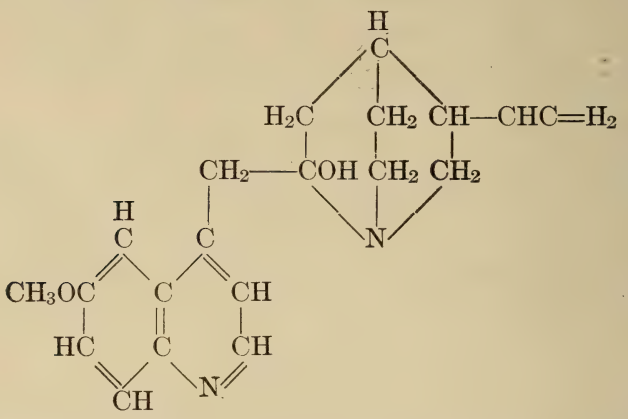
Cinchonamin, isomeric with cinchotin and cinchamin, is obtained from the bark of Remejia purdieana. It is dextrorotatory and melts 184–185° according to Pictet, though Chick gives 194°. It is readily soluble in the ordinary organic solvents except petroleum ether and is attacked by permanganate. It is seen commercially in the form of yellowish-white crystals and forms well-defined salts of which the nitrate is especially characteristic, being but slightly soluble in water and alcohol, and insoluble in dilute nitric acid. The compound is formed by dissolving the base in water containing a small quantity of hydrochloric acid, and adding a few drops of nitric acid.

Cinchonamin does not give the thalleoquin test. With vanadium sulphuric acid (Mandelin's reagent) it gives a bluish-violet color, changing to reddish violet and finally bluish green. With Froehde's reagent it gives a green tint turning yellowish green.

Quinin

This alkaloid is by far the most important of the cinchona group and is one of the most widely used of remedial agents. The analyst of drug products will frequently be called upon to identify it, to distinguish it from other bases of this group, and to determine it in mixtures with other alkaloids. It is not as easy of identification as strychnin, with which it is often mixed as its color reactions are less positive and those that it does possess are also common to other members of its own immediate family; but it is comparatively stable, and its solutions can be treated with reagents which will break up some of the more delicate alkaloids such as aconitin, atropin, and cocain, and by this means the latter if present may be removed, and quinin subsequently separated and purified.

Quinin differs constitutionally from cinchonin and cinchonidin by possessing an $—OCH_3$ group and from our present state of knowledge its formula may be written as follows:



Commercial quinin is apt to retain traces of cinchonin, quinidin, hydroquinin, and cinchonidin. It is lævorotatory while its stereoisomer quinidin is dextro. Quinin alkaloid, when precipitated out of solution, crystallizes as a white flaky or micro-crystalline powder; when obtained by evaporating an ethereal solution, it is a colorless, hard, varnish-like mass, and if in large amount with a crystalline appearance in places. It is odorless and has an intensely bitter taste. When freshly crystallized it contains three molecules of water, two of which are lost on heating to 100° and the third at 125° C. The anhydrous alkaloid melts 171–172° C. while the

crystalline body with three H_2O fuses at 57°. The anhydrous body is slightly soluble in cold water but somewhat more readily when heated, it is fairly soluble in benzol and glycerin and readily in ether, and alcohol. The dry alkaloid is but slightly soluble in petroleum ether, but when freshly precipitated it is taken up by this solvent to a considerable extent the same as is strychnin. It is very slightly soluble in 20 per cent potassium hydroxide and about as soluble in dilute ammonia as it is in water. Its aqueous solution is alkaline to litmus.

Quinin dissolves in sulphuric, acetic, and tartaric acids with a strong bluish fluorescence, discernible at great dilution and destroyed by the halogen acids. Quinidin, hydroquinin, hydroquinidin, and diquinicin give fluorescent solutions but quinamin, cinchonin, cinchonidin, cusconin, cuprein, and quinicin do not. This test will probably be the first indication of the presence of quinin that the analyst will have in working with an unknown mixture, and will be noted early in the systematic scheme of separation.

The thalleoquin test is a valuable confirmatory test for quinin. It is a test which is extremely delicate if carefully applied, but unless one is familiar with its vagaries it will often prove disappointing. Of all the well-known tests in alkaloidal chemistry this reaction will cause the analyst more uncertainty than any others. When there is a fair amount of the sample present it ought to be obtained without difficulty, but if there is only a minute quantity available the result will more than likely be negative. The directions in the Pharmacopœia are as follows: 1 mil of an aqueous solution of the alkaloid 1–100 containing just sufficient sulphuric acid for solution is treated with 2 mils bromine water and 1 mil dilute ammonia water which will produce a green color.

LaWall [1] has recently published a procedure by means of which he claims to be able to detect 1 : 200,000 of quinin by this test. According to the author 100 mils of a solution of the sulphate of the alkaloid to be tested at a dilution of 1 : 100,000 or 1 : 200,000 are poured into a Nessler tube, 5–10 drops of potassium bromate solution (0.5 gram potassium bromate, 10 mils hydrobromic acid 10 per cent and 90 mils water) added, the contents well mixed and then treated with 10 drops stronger ammonia water, which will produce a green tint in presence of quinin or other cinchona alkaloid giving the thalleoquin test. A modification of the thalleoquin test known as the erythroquin test and valuable as confirmatory evidence, consists in following the bromin water with a few drops of potassium ferro- or ferricyanide, and subsequently with ammonia, when a red coloration is produced instead of the green; on shaking with chloroform the coloring matter will dissolve and appears to better advantage especially in very dilute solutions.

[1] Amer. J. Pharm., 1912, 84, 484.

Buchbinder's directions for conducting this test are as follows: Have ready a test-tube (No. 1) containing 1 mil of chloroform and 3 mils of a saturated solution of potassium ferrocyanide. In another test-tube (No. 2) pour 5 drops of bromine water. Working as rapidly as possible, add to test-tube No. 2, 1 or 2 mils of the solution to be tested; immediately pour the contents of test-tube No. 2 into test-tube No. 1 and shake thoroughly. Add a little concentrated ammonia and shake again. A pink to red coloration will appear in the chloroform layer if quinin is present. If a precipitate forms on adding the solution to the bromin water, the test may possibly fail. In that case, repeat with a more dilute solution. The important point to be observed is the immediate removal of free bromin by the introduction of the ferrocyanide solution. Buchbinder claims that the test is sensitive to 0.02 mg. of quinin.

The thalleoquin test is also given by quinidin, cuprein, hydroquinin, hydroquinidin, and diquinicin, but not by quinamin, cinchonin, nor cinchonidin. Pilocarpin, cocain, atropin, codein, and strychnin do not interfere with the reaction but morphin does, as well as antipyrin and caffein, in certain proportions. Caffein can of course be removed by shaking it out of an acid solution and morphin may be eliminated if the quinin is separated by ether, in fact the quinin should be as pure as possible before applying this test.

When an alcoholic solution of iodin is added to an acid solution of quinin sulphate, a precipitate of the black or bronze iridescent iodo-sulphate is produced known as Herapathite. The directions for this test in the U. S. Pharmacopœia are as follows: 0.7 gram of quinin are dissolved in 15 mils of acetic acid, 6 mils alcohol and 0.5 mil sulphuric acid added and the solution heated to boiling, 7 mils of saturated solution of iodine in alcohol are added and the mixture allowed to cool when the Herapathite will gradually separate. It may be filtered off, washed, and recrystallized from hot alcohol. Quinidin, cinchonin, and cinchonidin also gives the iodosulphate, but that of quinin is much more insoluble in alcohol, and is soluble in water with difficulty.

0.2 gram of quinin dissolved in 1 mil of dilute sulphuric acid, diluted with water to 20 mils, the acid neutralized with ammonia, treated with 1 drop of hydrogen peroxide and 1 drop of copper sulphate 10 per cent and boiled, yields an intense red color which slowly changes to blue and finally to green. Quinidin also gives this test.

0.2 gram of quinin dissolved in 2 mils of concentrated sulphuric acid and treated with 0.5 mil hydrogen peroxide gives a deep yellow color gradually fading to light yellow which persists for a considerable time.

Quinin gives a well-defined precipitate with potassium chromate separating from a solution of 1–200; quinidin is also precipitated by this reagent as a fairly insoluble precipitate, but the chromates of cinchonin

and cinchonidin are much more soluble. The use of this compound has been proposed for the quantitative estimation of quinin, but its value is questionable and its use even for qualitatively distinguishing quinin from the other bases is not satisfactory.

Potassium iodide does not give a precipitate with quinin. This will distinguish quinin from quinidin and cinchonidin but not from cinchonin.

Potassium ferrocyanide gives a reddish-brown color, but no precipitate with dilute solutions of quinin; with quinidin a white flocculent precipitate is formed; with cinchonin and cinchonidin a white precipitate is thrown down soluble in excess.

Mercuric chloride does not precipitate dilute solutions of quinin until a considerable excess has been added while quidinin, cinchonin, and cinchonidin give immediate precipitates.

The ordinary alkaloidal reagents, Mayer's reagent, Wagner's reagent, potassium bismuthic iodide, phosphomolybdic and phosphotungstic acids, gold and platinic chlorides, and picric acid all give precipitates with quinin. With phosphotungstic acid a pink fluorescence is also noticeable.

Quinin picrate melts 125–126° C. This salt should always be made and identified when the identity of quinin is in question.

Salts of Quinin

Quinin forms a number of crystallizable salts, several of which are official, and these and many others are used medicinally. There is also a series of acid salts, usually much more soluble than the normal compounds, and on this account much preferred for certain purposes.

The most important salt is the sulphate, $(C_{20}H_{24}O_2N_2)_2H_2SO_4 \cdot +7H_2O$ which is perhaps the most extensively employed alkaloidal salt in the realm of medicine, rivaling morphin sulphate, cocain hydrochloride and strychnin sulphate, and possibly exceeded by the two former only on account of their vast illegitimate use. The commercial salt is seldom free from small quantities of allied bases. Cinchonidin is sometimes added in amounts of about 1 per cent in order to produce the fluffy appearance so much desired. The standard allows for minute quantities of these alkaloids and tests are included in the pharmacopœia for their detection if present in excessive amounts and as the drug analyst may be called upon to pass upon the purity of this body some detailed points about the various tests will be of interest.

This salt occurs in white lustrous or shining, fragile, needle-like crystals, very compressible and becoming dark if exposed continually to the light. When chemically pure the appearance is modified, the needles being less bulky and the salt is known as the "heavy sulphate." It is but sparingly soluble in cold water, requiring over 700 parts of the solvent to effect solution; in hot water it dissolves much more readily and on cool-

ing the crystals separate. In alcohol its solubility is about 1–65 cold and 1–3 boiling, and it dissolves with ease in a mixture of chloroform—absolute alcohol 2–1. It is sparingly soluble in chloroform and practically insoluble in absolute ether and petroleum ether. It is always slightly alkaline to litmus even when crystallized out of acid solutions.

The commercial salt always contains a little cinchonidin and hydroquinin and may also contain cinchonin, quinidin, and amorphous bases, and to detect the presence of undue quantities of these other alkaloids various tests have been proposed. The test which has been most extensively adopted for this purpose in the different pharmacopœias is the so-called ammonia test originally proposed by Kerner. It depends upon the fact that, while quinin sulphate is less soluble in water than the sulphates of the accompanying bases, quinin itself when freshly precipitated by ammonia is much more soluble in the latter than the other free bases. The procedure consists in treating 5 mils of an aqueous solution of the salt, saturated at 15° C., with 10 per cent ammonia water and noting the amount which will yield a clear solution. The limit varies, thus our own standard and the Italian is 7 mils, the French 5, the Netherlands 4.5 and the German 4. The results are only empirical as it is difficult to dissolve out cinchonidin sulphate from crystals of quinin sulphate, and cinchonidin sulphate forms a double salt with quinin sulphate in crystallizing. Tutin [1] has made an exhaustive study of this test working from the pure salt which he prepared by repeated crystallization and manipulation of the alkaloid through the *d*-camphorsulphonate and the *d*-bromcamphorsulphonate. He shows that the minimum amount of 10 per cent ammonia which will yield a clear solution at 15° C., with 5 mils of a solution of pure quinin sulphate saturated at 15° C. is 4.4 mils. He states that it is impossible to meet the German standard and that the French and Netherlands standards are more stringent than is desirable. It is evident then that our standard is the fairest where the manufacturer is concerned, and other things being equal, is safe for the consumer. Tutin belives that a minimum of 6 mils is a reasonable requirement, and leans towards the manipulation of the French Pharmacopœia, by which 1 gram of the salt is dissolved by boiling with 30 mils of water, cooled to 15° C., allowed to stand ½ hour and then 5 mils of the clear liquid treated with the ammonia. Tutin proves also that the basicity of the salt has the same effect as an impurity, and hence commercial salts which frequently contain a little free alkaloid, may appear to be far less pure than is actually the case. Finally alkaline sulphates if present will decrease the solubility of the quinin sulphate to such an extent that an impure product may appear purer than one which is strictly pure. The presence of inorganic salts may be ascertained by evaporating the aqueous solution to dryness and examining the residue for

[1] Amer. J. Pharm., 1912, 84, 484.

alkali bases and ammonia. Tutin concludes that this test is valueless as a means of ascertaining the purity of any salt of quinin, other than the normal sulphate, but in the case of this salt it is the only means of detecting hydroquinin without actually isolating that alkaloid.

The next scheme to be considered in the examination for impurities will be the test for the separate alkaloids as elaborated in the British Pharmacopœia.

Test for Cinchonidin and Cinchonin.—Dissolve 4 grams of the quinin sulphate in 120 mils of boiling water. Cool the solution slowly to 50° with frequent stirring. Separate, by filtration, the purified quinin sulphate which has crystallized out. Concentrate the filtrate by evaporation until it is reduced to 10 mils or less; transfer to a small stoppered flask and when cool, shake with 10 mils ether and half that amount of solution of ammonia. Set aside in a cool place for not less than twenty-four hours. Collect the crystals which consist of cinchonidin and cinchonin combined with quinin on a tared filter, wash with a little ether, dry at 100° and weigh. Those should not amount to more than 0.12 gram.

If this test is performed with ordinary ether an admixture of 7 per cent cinchonidin will escape detection, but if absolute ether is used 3 per cent of this alkaloid can be detected.

Test for Quinidin.—Dissolve 1 gram of the quinin sulphate in 30 mils of boiling water, cool, and filter. To the solution add solution of potassium iodide and a little 90 per cent alcohol to prevent the precipitation of amorphous hydriodides. Collect any separated quinidin hydriodide wash with a little water, dry, and weigh. The weight represents about an equal weight of crystallized quinidin sulphate.

Test for Cuprein.—Shake the recrystallized quinin sulphate obtained in testing the original quinin sulphate for cinchonidin and cinchonin with 25 mils of ether and 6 mils solution of ammonia, and to this ethereal solution separated, add the ethereal liquid and washings also obtained in testing the original sulphate for the two alkaloids just mentioned. Shake this ethereal liquid with 6 mils of 10 per cent sodium hydroxide, adding water if any solid matter should separate. Remove the ethereal solution, wash the aqueous solution with more ether and remove the ethereal washings. Add diluted sulphuric to the aqueous liquid heated to boiling until exactly neutral. When cold collect any crystallized sulphate of cuprein on a tared filter, dry and wash

Test for Cinchonin and Amorphous Alkaloids.—Dissolve 1 gram of quinin sulphate in 30 mils of boiling water. Add 1 gram sodium potassium tartrate. Allow to cool with frequent shaking and filter. The solution when evaporated to small bulk should give little or no precipitate with solution of ammonia.

Another type of test useful for detecting the presence of cinchonin

and quinidin has been proposed by Hesse and depends on the difference in their solubliities in chloroform. The quinin sulphate is dried at 100° C. and 1 gram agitated with 15 mils of alcohol-free chloroform, the solvent is filtered and 10 mils evaporated; which should not leave a residue of more than .035 gram. If the residue is crystalline and less than the above weight it may be tested for cinchonin and quinidin by warming it with 5 mils of water, adding 0.5 gram of sodium potassium tartrate, cooling, filtering, and treating the filtrate with an equal volume of ammonia water. If quinidin or cinchonin are present a precipitate will be formed. Cinchonidin sulphate if present will swell up into bulky needles when treated with chlorofrom, but it does not dissolve, and the solvent may be separrated by pressure.

If a solution of quinin sulphate is treated with an excess of potassium chromate and allowed to stand several hours, the quinin is almost entirely precipitated. On filtering and adding sodium hydroxide to the filtrate the solution will remain clear if the quinin is pure, but will become turbid in the presence of 1–2 per cent of allied alkaloids.

The examination of quinin sulphate for amorphous alkaloids has been studied by DeVrij, who recommends adding ammonia to an acid solution of the salt and then shaking out with ether in order to obtain the free alkaloids. After evaporating the solvent the residue is treated with N/10 oxalic acid in sufficient amount to convert the alkaloids into neutral oxalates, the liquid is evaporated over the steam-bath and the residue dried. The neutral oxalates are then dissolved in chloroform and the solution filtered and treated with a few drops of water when crystals of quinin oxalate will appear in the solvent. In the case of a pure sample the water will remain clear and uncolored, but if amorphous alkaloid is present the water will be colored yellow.

A number of methods have been proposed for determining the purity of quinin sulphate by reference to its rotatory power, but there are so many conditions which impair the accuracy of any observations of this property that the writer has decided to omit them.

The determination of the amount of alkaloid in a sample of quinin sulphate is readily effected by dissolving a weighed quantity in water slightly acidulated with sulphuric acid, adding a slight excess of ammonia and shaking out three times with ether. The combined ethereal solutions are washed with water and the solvent solution filtered into a tared dish, the ether evaporated and the residue brought to a constant weight at 100° C. If desired the gravimetric estimation may be checked titrimetrically and for this purpose attention is called to Elvove's procedure;[1] about 0.2 gram of the alkaloidal residue is dissolved in an excess of dilute hydrochloric acid 4 per cent, the liquid completely evaporated, the sur-

[1] Hyg. Lab. U. S. P. H. & M. H. Service Bul. 54.

face film being broken up from time to time with a glass rod, the residue allowed to remain in the water-bath for three hours, then dissolved in 10–20 mils of water, 3 drops phenolphthalein added, and titrated with standard sodium hydroxide until the solution develops a faint pink color. At this point one more drop of the indicator is added and if the solution at once assumes a very deep pink color, standard acid is added until the color remaining is only light pink, the alkali equivalent of the acid just added being deducted from the total alkali added first. Two molecules of sodium hydroxide are equivalent to one molecule of quinin. The method is applicable to quinidin, cinchonin, and cinchonidin.

Iron and Quinin Citrate

The Pharmacopœia formerly recognized two products under this title, one readily soluble and the other slowly soluble, and both containing, 11.5 per cent quinin and 13.5 per cent metallic iron. The ninth revision, however, has deleted the less readily soluble compound. These bodies are really mixtures of iron citrate and quinin citrate containing more or less ammonium citrate. The more readily soluble of the two occurs in thin transparent scales of a greenish-golden-yellow color and the other in reddish-brown scales. They are both partially soluble in alcohol. The iron does not respond to the ordinary qualitative tests, but if the quinin is precipitated by ammonia and the filtrate acidulated with hydrochloric acid the Prussian blue reaction will be given with potassium ferrocyanide. The official assays for quinin and iron are as follows:

Dissolve about 1 gram of Iron and Quinin Citrate, accurately weighed, in 20 mils of distilled water in a separator, add 5 mils of ammonia water and 10 mils of chloroform, and shake the separator for one minute. Allow the liquids to separate, draw off the chloroform layer through a small filter moistened with chloroform, into a tared dish, and shake the residuary liquid a second and a third time with portions of 10 mils each of chloroform, passing the chloroform through the filter each time and finally washing the filter with 5 mils of chlorofrom. Evaporate the combined chloroform solutions, redissolve the residue in 3 mils of alcohol, again evaporate and then dry the residue to constant weight at 100° C. This residue corresponds to not less than 11.5 per cent of the amount of Iron and Quinin Citrate taken for the assay and conforms to the identity tests under Quinin.

Assay for Iron.—Heat the aqueous liquid, from which the quinin has been removed in the manner just described, on a water-bath, until the odors of chloroform and of ammonia have disappeared, allow to cool, and dilute with distilled water to a volume of 25 mils. Transfer the liquid to a glass-stoppered bottle, add 15 mils of hydrochloric acid and 3 grams of potassium iodide, and, after securely closing the bottle, allow the mix-

ture to stand for thirty minutes at 40° C. Then cool and titrate with sodium thiosulphate, using starch as indicator. It shows not less than 13 per cent of Fe.

Each mil of N/10 sodium thiosulphate used corresponds to 0.005584 gram of Fe. Each gram of Iron and Quinin Citrate corresponds to not less than 23.3 mils of N/10 sodium thiosulphate.

Quinin and Urea Hydrochloride

$$C_{20}H_{24}N_2O_2 \cdot HCl + CH_4N_2O \cdot HCl + 5H_2O.$$

This salt in aqueous solution is used to a limited extent for hypodermic injections and exerts an anesthetic action similar to that of cocain. It occurs in white crystals which are very soluble in water.

QUINIDIN

Quinidin is the stereoisomer of quinin. It rotates the plane of polarized light to the right, melts 168–171.5°, the latter figure being obtained with the anhydrous alkaloid. It crystallizes from alcohol and ether with water of crystallization and may be rendered anhydrous by heating to 120°. It is readily soluble in ether and alcohol, somewhat soluble in chloroform and benzol, and slightly soluble in water,

It resembles quinin in its reactions, but differs from quinin in giving a very sparingly soluble precipitate with potassium iodide. It also gives a permanent bulky precipitate when its solution is treated with chlorin water, potassium ferricyanide, and ammonia. Quinidin picrate melts 137–138° C. Quinidin is marketed in the form of the sulphate which contains two molecules of water. This salt is soluble in 20 parts of chloroform. It may be examined for other alkaloids by dissolving 0.5 gram in 10 mils water and adding .5 gram neutral potassium iodide, stirring, cooling, and filtering after half an hour from the precipitated hydriodide; the filtrate is then treated with 1–2 drops of ammonia water and if a precipitate is thrown down the presence of other alkaloids is indicated.

The commercial salt usually contains traces of hydroquinin and hydroquinidin.

0.2 gram quinidin treated with 2 mils concentrated sulphuric acid and 0.5 mil hydrogen peroxide gives a yellow color turning to a deep orange and gradually fading to colorless.

HYDROQUININ AND HYDROQUINIDIN

The two alkaloids differ constitutionally from quinin and quinidin by containing two more hydrogen atoms, and occur with them in the commercial salts. They are stable to permanganate and may be separated

by treating the mixture with this reagent which destroys quinin and quinidin. Hydroquinin is lævorotatory and in the anhydrous state melts 172°. Hydroquinidin is dextrorotatory and melts 166–167°. They both give fluorescent solutions with acids and respond to the thalleoquin tests.

QUINAMIN AND CONQUINAMIN

These two isomeric bodies occur in a number of different species of Cinchona and are probably present in small amounts in commercial Cinchona alkaloids. They are both dextro, the latter more strongly, and are soluble in the ordinary organic solvents. Quinamin melts 172° and conquinamin 121–123°. Quinamin hydrochloride reduces gold chloride solution.

Mulliken describes the following reaction of quinamin. If a solution of the salt strongly acidified with sulphuric acid is smeared over white paper and held over a watch glass containing sulphuric acid and potassium chlorate, the lines become olive green in color and on exposure to air turn blue.

CUPREIN

Cuprein occurs in the bark of Remijia pedunculata and in other species of Remijia. It differs from most of the other alkaloids of this family in uniting with alkalies and some of the less basic elements to form definite soluble salts, this property being due to the presence in its molecule of an hydroxyl group having a phenolic character. Its alcoholic solution gives a reddish-brown color with ferric chloride. It is sparingly soluble in ether and chloroform, but when precipitated from its acid solution by ammonia can be removed from the mixture by these solvents. Fixed alkalies dissolve the precipitated alkaloid, and ether cannot remove it from this solution.

Cuprein melts 198° after drying at 125° C., is lævorotatory, gives the thalleoquin test, but its acid solutions do not fluoresce. It forms stable crystalline compounds with the cinchona bases, one of which, homoquinin, has been carefully studied. The latter is obtained when molecular proportions of quinin and cuprein are dissolved in dilute acid, precipitated with ammonia and shaken out with ether, which leaves the double body on evaporation. Its salts differ from those of either of its two components. Homoquinin may be separated into its constituents by treating an acid solution with excess of fixed alkali and shaking out the quinin with ether, the cuprein remaining in solution.

Cuprein forms two classes of salts the normal being but slightly soluble in water.

The relationship of cuprein to quinin is the same as that of phenol to its methyl ether. The transformation of cuprein into quinin is effected

by treating a solution of cuprein in methyl alcohol with sodium and then with methyl iodide, the temperature, starting from zero, being gradually raised during several hours. Under these conditions quinin itself is not formed, but quinin mono- and dimethyl iodides. When operating in a closed vessel with an excess of methyl iodides only the latter body is produced. Methyl-cuprein-dimethyl iodide agrees in all its properties with quinin-dimethyl iodide, as is shown by the following figures:

	Quinin dimethyl iodide	
	Synthetical	Natural
Melting-point (with partial decomposition)	167–168° C.	167–168° C.
Rotatory $(a)_D$	—150.8	—151.6
Percentage of iodine	41.34	41.77

If the methyl iodide be replaced by methyl chloride, free quinin is formed. A mixture of one molecule of cuprein, one atom of sodium and one molecule of methyl chloride dissolved in methyl alcohol, is heated to 100° C. in a closed tube. The product of the reaction is evaporated to dryness, washed with a dilute soda solution in order to remove any unaltered cuprein, and finally extracted after conversion into sulphate of quinin, the product resembles the natural article in all respects.

ALKALOIDS OF THE CUSCONIN CLASS

This group is found in Cusco bark and probably in other species of Remijia. Chick gives them all the same formula, $C_{22}H_{26}N_2O_4$, but Pictet gives one more carbon atom to aricin, cusconin, and concusconin. Pictet's summary of their characteristics is as follows:

Chairamin occurs in needles or prisms, which in the hydrous condition melt at 140°, in the anhydrous at 233°. It is dextrorotatory.

Chairamidin is amorphous and dextrorotatory and in the anhydrous condition melts at 126–128°.

Conchairamin is a very weak base, dextrorotatory, melting in the anhydrous condition at 120°.

Conchairamidin occurs in lævorotatory needles melting in the anhydrous condition at 114–115°.

Aricin crystallizes from alcohol in prisms melting at 188°. It is lævorotatory in neutral solution, inactive in hydrochloric acid.

Cusconin crystallizes in prisms melting at 110° and is lævorotatory.

Concusconin is a dextro base melting at 206–208°.

Cuscamin and cuscamidin have been mentioned, but a description of their properties is lacking.

QUINICIN AND CINCHONICIN

Quinicin and cinchonicin are amorphous bases resulting respectively when quinin and cinchonin are heated under certain conditions. Quinicin is dextrorotatory, gives the thalleoquin reaction, is readily soluble in alcohol and ether, and forms a number of crystalline salts. It is not precipitated by Rochelle salt, but gives insoluble precipitate with potassium thiocyanate, and a white precipitate with hypochlorites. Cinchonicin resembles the above base in most of its properties but does not give the thalleoquin test. Quinicin melts 60° and cinchonicin 58–59° C.

DIQUINICIN AND DICINCHONICIN

These two bases, also amorphous, make up the greater part of quinoidin. The former may be considered an anhydride of quinin or quinidin and the latter as a double molecule of cinchonin or cinchonidin, though this has been disputed. Diquinicin gives the thalleoquin test and its acid solutions are fluorescent, dicinchonicin does not answer these tests.

DeVrij has worked with the amorphous bases and distinguishes them by the behavior of their neutral oxalates rendered anhydrous at 100° C. Quinicin oxalate is almost insoluble in cold chloroform, and though it dissolves in the hot liquid it is deposited again on cooling. Cinchonicin oxalate is readily soluble in cold chloroform and on adding a few drops of water the solution solidifies. The oxalates of the natural amorphous bases dissolve easily in chloroform and the solution does not solidify on adding water.

Quinoidin is the name given to a brownish-black resinous-appearing mixture of amorphous cinchona alkaloids which has a somewhat limited use in manufacturing pharmacy. The alkaloids composing it are those left in solution after the crystalline alkaloids have been removed. It is soluble in dilute acids, alcohol, and chloroform. Several of its salts, including the borate, citrate, hydrochloride, sulphate, and tannate are commercial articles.

EXAMINATION OF CINCHONA BASES FOR IDENTIFICATION

Though these alkaloids are of common occurrence in medicinal preparations, the individuals are among the most unsatisfactory of chemical bodies to identify. They follow one another closely in their solubilities, and it is next to impossible to effect a complete isolation of any one by ordinary analytical reactions. We state that cinchonin and cinchonidin do not give fluorescent solutions with acids, and yet there is probably no commercial salt of these alkaloids which will not give a fluorescent solution. It is well known that these same alkaloids do not give the

thalleoquin test, but unless one is fortunate in his manipulation, he will often fail to get this reaction with quinin and quinidin, and when working with small quantities perhaps be unable to obtain it at all. Any alkaloidal residue obtained from a preparation containing an extract of cinchona will give a fluorescent solution with dilute sulphuric acid, and will more than likely contain quinin, cinchonin, cinchonidin, and perhaps quinidin in varying proportions. In fact in many instances the worker can report the presence of cinchona alkaloids, and that is about as far as he can go. Any method of separation of the main alkaloids requires a sample which, in quantity, is almost prohibitive unless it happens to be a " pure " salt, and is of no value for the relatively small residues which one ordinarily obtains.

If the residue in question is transparent, colorless, and hard like a varnish with perhaps here and there the appearance of a crystalline form, it probably consists entirely of quinin. A good thalleoquin test will indicate quinin or quinidin. If a neutral solution gives a copious precipitate with potassium iodide and the filtrate yields but a small quantity of alkaloid after treatment with alkali and shaking out with ether, the substance is chiefly quinidin. Cinchonidin will give a curdy precipitate under similar conditions while that obtained with quinidin will be granular if the original material is pure, but of course cinchonidin does not respond to the thalleoquin test.

Quinin and quinidin when dissolved in concentrated sulphuric acid and treated with 0.5 mil hydrogen peroxide give deep-yellow solutions, becoming orange in the case of quinidin and then gradually fading to yellow, the quinin solution holding its color over an extended period. When cinchonin or cinchonidin are treated under like conditions they give light-yellow solutions which soon fade.

The iodosulphates of the cinchona base differ considerably in their solubilities and appearances; quinin iodosulphate is black and iridescent and but slightly soluble in water or dilute alcohol, quinidin iodosulphate is reddish brown and much more soluble, so that it often takes considerable time to precipitate; the cinchonidin compound is slightly less soluble and the cinchonin compound more soluble than that of quinidin.

Potassium ferrocyanide gives a white flocculent precipitate with quinidin, a reddish-brown color with quinin, and a white precipitate soluble in excess with cinchonin and cinchonidin.

The directions of rotation of polarized light is to the right with quinidin and cinchonidin and to the left with quinin and cinchonin, but this property is of little value as a means of identification unless the sample is comparatively large.

It will be noted from the above paragraphs that the tests for cinchonin and cinchonidin are much less positive than those for quinin and quinidin.

If one has sufficient residue it should be carefully purified, heated to 125°, allowed to stand in a desiccator and its melting-point taken. Quinin melts at 171–172°, quinidin 168–171.5°, cinchonin 250–265°, and cinchonidin 202–203°. In all cases the picrate should be prepared and its melting-point determined.

With the above notes in mind the examination of an alkaloidal residue, suspected of being composed of one or more members of the Cinchona group, may take the following course. If the sample under consideration contains an extract of any of the Cinchonas or Remijias, a solution of the alkaloids in dilute sulphuric acid will almost invariably have a bluish fluorescence and the alkaloidal residue obtained therefrom will contain several different alkaloids in varying proportions. If there is sufficient quantity for preliminary tests, small portions of the residue should be treated separately with bichromate and sulphuric acid, formaldehyde-sulphuric acid, nitric acid and evaporated and the residue treated with a few drops of alcoholic potash in order to insure the absence of some of the main groups of alkaloids. The next step should be the determination of the melting-point as described in the preceding paragraph. Then the test with sulphuric acid and peroxide should be tried, followed by the thalleoquin, herapathite, the potassium iodide and the ferrocyanide tests and the melting-point of the picrate determined and with the data obtained the identity of the individual can be very closely established. The various other properties of the individual can then be tested and checked with the descriptive data.

In order to effect a separation of the main alkaloids when they occur together, Chick, in the new edition of Allen, describes DeVrij's scheme, which was also used in the former edition. It will be described here in brief, as it is a valuable method, not only for separating the alkaloids themselves, but as an aid in establishing the identity of an individual. The sample, which should not amount to less than 2 grams, in a state of fine division, is treated in a small Erlenmeyer flask with ten times its weight of absolute ether and well shaken, the flask stoppered and allowed to stand for twelve hours. It is then filtered into a tared dish, and the residue washed with a small quantity of ether, and the filtrate evaporated to dryness and weighed. This residue consists of quinin, quinamin, amorphous alkaloids, and traces of quinidin and cinchonidin, the portion insoluble in ether being composed of cinchonin, cinchonidin, and quinidin. The residue containing the quinin is then dissolved in 10 parts of 50 per cent alcohol acidified with 1/20 of sulphuric acid and treated with an alcoholic solution of iodin as long as a precipitate is obtained, avoiding an excess of the reagent. If much quinin is present a black precipitate of herapathite is immediately produced but if the quantity is small some time is required for its appearance, and in this case only a small quantity

of iodin should be added and the solution well stirred and allowed to stand twelve hours. The precipitate is then filtered off, washed with strong alcohol, decomposed with sulphurous acid and the quinin liberated with ammonia and extracted with ether. The alcoholic filtrate and washings are then rendered colorless with sulphurous acid and carefully neutralized with sodium hydroxide, the alcohol evaporated, the residue made alkaline and shaken out with chloroform. After evaporating the solvent the amorphous alkaloids will dissolve in a limited amount of ether, leaving most of the quinidin and cinchonidin behind.

The bases which were insoluble in ether are then dissolved in dilute sulphuric acid, the solution exactly neutralized with sodium hydroxide, an excess of saturated solution of Rochelle salt added, cooled to 15° C. and allowed to stand for one hour. If cinchonidin is present, crystalline streaks of the tartrate form, the solution is filtered off and washed with 5 per cent solution of Rochelle salt. The filtrate is concentrated to its original volume, a drop of acetic acid is added and an excess of a saturated solution of potassium iodide. The mixture is allowed to stand for two hours at 15° C. with frequent stirring, and if quinidin is present, a precipitate of the hydriodide is formed which is filtered, washed with cold water, and the alkaloid recovered by treatment with ammonia and agitation with chloroform. The filtrate and washings from the hydriodide precipitate is then made alkaline with sodium hydroxide and the cinchonin extracted with chloroform.

As illustrative of the peculiarities of this group it may happen that when working with the mixed alkaloids an ethereal solution will yield a quantity of a molecular combination, for instance, of quinin and quinidin. When these crystals are dissolved in sufficient sulphuric acid to form the neutral salt, quinin sulphate will crystallize and the mother liquor will contain quinidin sulphate. The crystalline compound above mentioned will be but slightly soluble in ether, though it is more soluble in ethereal solution of quinin and such a solution frequently exhibits supersaturation, remaining clear for some time and then suddenly giving a cloud of crystals.

Quantitative Estimation.—The quantitative estimation of the individuals of this group presents little difficulty; the alkaloids are comparatively stable, they will stand considerable manipulation, and it is only when they occur together with some strong base like strychnin that their separation becomes involved.

In order to determine quinin or the allied bases in tablet triturates or plain compressed tablets of the sulphate or bisulphate, the sample amounting to 10 or 25 tablets should be introduced into a 250-mil separator of the Squibb type, moistened with water, shaken until disintegrated and then made alkaline with ammonia. About 25 mils of ether

COMPARATIVE REACTIONS OF THE IMPORTANT CINCHONA BASES

Alkaloid	Quinin	Quinidin	Cinchonin	Cinchonidin	Cuprein
Melting-point	171–172°	168–171.5°	250–265°	202–203°	198°
Optical rotation	−145.2 in 97% alcohol ($c=2$)	+236.8 in 97% alcohol ($c=2$)	+226.5 in 97% alcohol ($c=0.5$)	−70° in chloroform ($c=4$)	−175.3° in 97% alcohol ($c=1.5$)
Thalleoquin test	Positive	Positive	Negative	Negative	Positive
Potassium iodide	No precipitate	White sandy precipitate	No precipitate	White flocculent precipitate	
Herapathite	Black, very insoluble	Reddish brown	Brown. Quite soluble	Brown. Fairly soluble	
Potassium ferrocyanide	Reddish-brown color	White flocculent precipitate	White precipitate soluble in excess	White precipitate soluble in excess	
Potassium chromate	Yellow precipitate	Yellow precipitate	Yellow precipitate, slowly forming	No precipitate	
Rochelle salt	No precipitate	No precipitate	No precipitate	White feathery precipitate	
Gold chloride	Yellow precipitate	Yellow precipitate	Yellow precipitate	Yellow precipitate	
Phosphomolybdic acid	Yellow precipitate	Orange precipitate	Yellow precipitate	Yellow precipitate	
Phosphotungstic acid	White precipitate. Pink fluorescence	White precipitate	White precipitate	White precipitate	
Picric acid	Yellow precipitate, melting 125–6°	Yellow precipitate, melting 137–8°	Yellow precipitate, melting 193–4°	Yellow precipitate, melting 208–9°	
Tannic acid	White precipitate	White precipitate	White precipitate	White precipitate	
Platinic chloride	White precipitate	White precipitate	White precipitate	White precipitate	
Bromine water	Yellow precipitate	White precipitate dissolving to yellow sol.	Yellow precipitate	White precipitate dissolving to pinkish sol.	
Potassium bismuthic iodide	Dark-brown precipitate	Brown precipitate	Brown curdy precipitate	Brown precipitate	

are added and the separator shaken, the aqueous mixture drawn off into another separator and the operation repeated twice, which is sufficient to remove all of the alkaloid. The ethereal solution may then be concentrated to about 50 mils and shaken out three times with 15 mil portions of dilute sulphuric acid, the quinin liberated from the acid with ammonia and shaken out three times with 25-mil portions of ether, the combined ether shake-outs washed with water, filtered into a tared dish, evaporated, and the residue weighed. This residue is sufficiently pure to render a titration unnecessary.

With pills and coated tablets the disintegration will probably be slower, but the general plan described above should be followed, though to avoid emulsification the first extraction may be accomplished with Prolius mixture. If Prolius is used the solvent should be evaporated and the residue dissolved in dilute acid as the removal of an alkaloid from Prolius solution by acid is unsatisfactory.

Quinin sulphate in capsules is usually mixed with milk sugar. The contents of the capsules should be poured into a separator and treated as under tablet triturates.

When a liquid preparation is under examination and it has been found that cinchona bases are the only alkaloidal constituents, a quantity amounting to 25 or 50 mils should be washed into a separator, treated with excess of ammonia and shaken out with ether or Prolius, depending on its behavior, and the alkaloids purified in the usual way. Some liquid preparations contain but small quantities of the alkaloids, and for products of this type, which include various bitters and quinin whiskies, a generous sample amounting from 100–500 mils should be concentrated to about 50 mils, then made alkaline and the determination continued.

Where quinin has been identified in tablets which also contain resinous drugs, the sample should be thoroughly ground up in a mortar and extracted four or five times with alcohol, the alcoholic solution evaporated in the presence of a little acidified water, and when the alcohol has been driven off sufficiently to precipitate the resins, the liquid is filtered into a separator and the dish and filter washed three times with 15-mil portions of hot dilute acid. From this point the determination may follow the regular scheme.

Quinin will often be found in combination with the belladonna alkaloids and with strychnin and less often with the opium and ipecac alkaloids. The manipulation of a product in which the belladonna alkaloids have been found must be carried out with care as these bodies are readily decomposed. In order to obtain the total alkaloidal content the pill or tablet should be ground up in a mortar and extracted with alcohol, the solvent cautiously evaporated until the liquid is in small bulk, treated with dilute sulphuric acid and filtered into a separator. Ammonia is then

added in excess and the alkaloids shaken out with chloroform, the latter is filtered into a tared dish, evaporated, the residue dried in a vacuum desiccator and weighed as total mixed alkaloids. The quinin may then be estimated by the same procedure recommended for separating cocain and strychnin described in detail under Nux Vomica alkaloids, page 52, the belladonna alkaloids being thereby destroyed and the quinin being recovered.

If the analyst is working with a quinin morphin mixture the preliminary procedure will be similar to that already detailed, and then the quinin may be obtained alone by shaking it out with ether from a solution made slightly alkaline with fixed alkali and the morphin obtained subsequently after acidulating, rendering ammoniacal and shaking out five times with chloroform-alcohol 2–1.

QUININ FROM STRYCHNIN

No very satisfactory method has yet been evolved for accurately and completely separating quinin and strychnin. This important mixture is quite common. It has been proposed to remove the strychnin as the ferrocyanide, but the precipitate invariably carries down with it a portion of quinin. Another procedure involves precipitating the quinin as oxalate, but it has been found impossible to wash out the strychnin without dissolving some of the quinin and it is impossible to separate the latter by means of a solvent when it occurs in a drug mixture with strychnin.

The methods in use for the separation and determination of quinin and strychnin in admixture are described under the Nux Vomica Alkaloids.

The following titration method was devised by Buchbinder for mixtures of quinin and strychnin, and the author believes that the same procedure might be used for mixtures of quinin with such other alkaloids as give a neutral (to methyl red) hydrochloride and are not effected by treatment with acids.

Dissolve the isolated alkaloid in alcohol; add a few drops of concentrated hydrochloric acid and evaporate to apparent dryness on the water-bath. Dry in an oven at 110° until there is no reddening of a wetted piece of blue litmus paper held over it for a minute while in the oven. Dissolve in a little water and titrate with N/50 alkali.

There is formed the dihydrochloride of quinin which is acid toward methyl red, the monohydrochloride being neutral. Difficulty is experienced in the recognition of the end-point, and this uncertainty is even more pronounced with the chloride than with the sulphate. However, with the aid of blanks, and after experience even without their aid, an accurate determination can be made.

One mil of N/50 acid or alkali = 6.49 mg. anhydrous quinin = 7.57 mg. quinin + $3H_2O$ = 8.73 mg. quinin sulphate + $7H_2O$.

Nishi [1] suggested a method for determining quinin by precipitating it as the citrate out of ethereal solution by means of an ethereal solution of citric acid, and Cockburn and Black [2] worked with it and considered it very accurate. The precipitated citrate after standing twenty-four hours is filtered onto asbestos, washed with ether and weighed.

SEPARATION OF THE CINCHONA BASES

Leger [3] has worked on the determination of quinin in mixtures with other cinchona alkaloids and proposed a method which he considers very accurate for mixtures of the sulphates of quinin, cinchonidin, and cinchonin. The total alkaloids in the form of basic sulphates are treated with a boiling mixture of 5 mils of water and 75 mils of a solution of quinin sulphate saturated in the cold until completely dissolved and then set aside for twenty-four hours. In this way the sulphates of quinin and cinchonidin are separated and the sulphates of the other bases remain in the mother liquor. The crystalline sulphates are then filtered onto a Gooch, washed with saturated quinin sulphate and finally with 2 mils water, then dried spontaneously in the air, then at 30° C. and weighed. 0.7 gram is then brought into solution in 40 mils of a boiling saturated solution of the tartrates of quinin and cinchonin, 2 mils of a sodium-potassium tartrate 35 per cent are added, and after twenty-four hours the precipitate of double tartrates is collected on two counterpoised filters, washed first with saturated solution of cinchonidin and quinin tartrate, and then with 5 mils of water. The filters are drained and pressed between bibulous paper, the contents withdrawn and the filters and tartrates dried separately in the air and weighed. The index of rotation is then determined according to Ondemann's formulæ,

$$215.8 \times x \times 131.3(100-x) = 100 \times am,$$

in which am = the observed rotation of the mixed tartrates. Hence $x = \frac{100am - 13130}{215.8 - 13.3}$, in which 215.8 is the rotatory index of quinin tartrate and 131.3 that of cinchonidin tartrate. The quantity of quinin tartrate $T.\ Q.$ in the mixed tartrates $T.M.$ will be therefore

$$T.\ Q. = \frac{T.M.\ (100\ am - 13130)}{100(215.8 - 131.3)},$$

and the corresponding amount of quinin Q will be:

$$Q = \frac{324 \times T.M.(100am - 13130)}{408 \times 100(215.8 - 131.3)},$$

324 being the molecular weight of quinin and 408 that of its tartrate.

[1] Analyst, 1909, 34, 443. [2] Analyst, 1911, 36, 396.
[3] J. Pharm. Chim., 1904, 19, 427.

QUININ DERIVATIVES

Aristochin. Diquinin carbonic ester. Aristoquin

$$CO(C_{20}H_{23}N_2O_2)_2$$

Aristochin occurs as a white, tasteless powder melting at 189° C., insoluble in water, sparingly soluble in alcohol and ether, and somewhat soluble in warm alcohol and chloroform. It combines with one and two molecules of hydrochloric acid to form soluble salts. Acids gradually decompose it with liberation of quinin. It is prepared by treating quinin dissolved in pyridin or chloroform with carbonyl chloride, or by heating together quinin and phenol carbonate in the proportion of 2–1.

Chinaphenin

Phenetidin quinin carbonic acid ester.

$$CO(NHC_6H_4OC_2H_5)(C_{20}H_{23}N_2O_2)$$

This derivative is prepared by the action of quinin on *p*-ethoxyphenyl carbonic acid chloride. It is a white, odorless, tasteless powder, difficultly soluble in water, but readily soluble in alcohol, ether, chloroform, and benzol, and dissolving in acids to form salts. It is decomposed by acids with liberation of quinin. It gives the thalleoquin test and a yellow iodosulphate.

Euquinin. Quinin Ethyl Carbonate. Euchinin

$$C_2H_5O\cdot CO\cdot OC_{20}H_{23}N_2O$$

Alkyl esters of the cinchona alkaloid carbonic acids are prepared by heating the alkaloids with an alphyl ester of an alkylcarbonic acid. Thus, the ethyl ester of quinin carbonic acid is obtained by heating quinin with phenylethyl carbonate, dissolving the product in benzene, removing phenol by dilute ammonia, extracting the ethyl ester by a dilute acid, and precipitating by alkali. The product, $C_2H_5O\cdot CO\cdot OC_{20}H_{23}N_2O$, forms white needles, which melt at 95° C., sparingly soluble in water but readily soluble in alcohol, ether, and chloroform. It is slightly alkaline in reaction and forms bitter salts with acids. Its solution in dilute sulphuric acid is strongly fluorescent, it gives the thalleoquin test, but not the herapathite reaction. On warming with sodium hydroxide and iodine, iodoform is produced.

Euquinin is practically tasteless and forms a tasteless tannate.

Saloquinin

Quinin Salicylic ester. Salochinin. Salicylquinin.

When quinin is heated with phenyl salicylate (salol) in an oil-bath

at 170–190° C., phenol distills and the quinin ester of salicylic acid remains. The product is dissolved in chloroform and shaken with 1 per cent acetic acid in order to remove unchanged quinin.

$$OH \cdot C_6H_4 \cdot CO \cdot OC_6H_5 + C_{20}H_{24}N_2O_2 = C_6H_5 \cdot OH + OH \cdot C_6H_4 \cdot CO \cdot OC_{20}H_{23}N_2O.$$

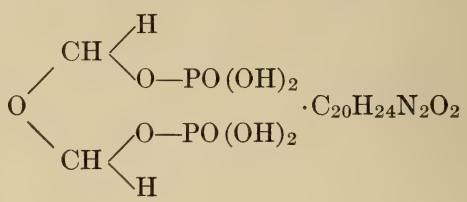
The compound is a white crystalline, odorless and tasteless powder melting at 140° C., soluble in chloroform, hot alcohol, and benzene, little soluble in ether and cold alcohol. Ferric chloride colors the alcoholic solution reddish-brown. The corresponding cinchonidin compound melts at 65–70° C., its acid sulphate forms white needles which melt at 165° C. Its acid solutions are precipitated by alkalies and the usual alkaloidal reagents.

Saloquinin salicylate is prepared by the addition of salicylic acid to a hot alcoholic solution of saloquinin. It is a white tasteless powder melting 182–183° C., sparingly soluble in water, soluble in benzol, chloroform, and hot alcohol.

Acid quinin dibromsalicylate, $C_{20}H_{24}N_2O_2 2(C_6H_2Br_2OH \cdot COOH)$, known as Bromoquinol, occurs as yellowish crystals melting 197–198° C. and soluble with difficulty in water, alcohol, and ether.

Quinin phytin

This product is obtained by neutralizing anhydroxymethylene-diphosphoric acid (phytin) with quinin and evaporating *in vacuo*.



It is a yellowish crystalline powder, bitter, soluble in water with fluorescence, insoluble in alcohol, ether, benzol, and chloroform. It is an antipyretic.

Quinin Lygosinate

$$CO(CH : CH \cdot C_6H_4 \cdot C_{20}H_{24}N_2O_2)_2$$

Quinin lygosinate is prepared by the reaction of quinin hydrochloride with sodium lygosinate and is a quinin compound of dioxy-dibenzal-acetone. It is a bright orange-red amorphous powder, with a faint odor and bitter taste, melting at 114° C., slightly soluble in water, readily in alcohol, chloroform, and benzol, and decomposed by acids and alkalies.

It dyes cotton a bright yellow. On warming, the odor of benzaldehyde is developed. It may be separated into its constituents by shaking with alkali, removing the liberated quinin with ether, and on acidifying the lygosin separates as a yellow oil.

It is employed as a styptic and bactericide, and applied as a dusting powder, on gauze, and in glycerin suspension.

Guaiaquin.—Quinin Guaiacolbisulphonate,

$$C_6H_4O_2CH_3HSO_3C_{20}H_{24}N_2O_2,$$

is a yellow, bitter powder soluble in water, alcohol and dilute acids.

Guaiaquinol.—Quinin Dihydrobromoguaiacolate, $C_{20}H_{24}N_2O_2 \cdot 2HBr \cdot C_6H_4OHOCH_3$, occurs as yellow hygroscopic crystals, readily soluble in water.

Quinaphthol.—Quinin betanaphthol monosulphonate,

$$C_{20}H_{24}N_2O_2(OHC_{10}H_6SO_3H)_2,$$

is a yellow crystalline powder, melting 185–186° C., soluble in alcohol and hot water.

Quinin Eosolate $(C_9H_7S_3O_{12})(C_{20}H_{24}N_2O_2)$, is the neutral salt of trisulphoacetyl guaiacol, a yellow, bitter amorphous powder, soluble in alcohol and slightly in water.

Quinin Ethyl Sulphate or Sulphoninate $C_{20}H_{24}N_2O_2 \cdot C_2H_5SO_4$, occurs in white crystals readily soluble in water.

J. Hesse has recently prepared a new compound of phenol with quinin bisulphate. If carbolic acid be added in equivalent proportion to a hot aqueous solution of quinin bisulphate, on cooling at first an oily mass separates out, above which delicate white needles are gradually formed, of the composition $C_{20}H_{24}N_2O_2 \cdot SO_3 \cdot C_6H_6O + 3H_2O$. This compound is very unstable. If it be dissolved in hot water, on cooling the first named normal salt crystallizes out. Quite in accordance with this is the behavior of the acid quinin resorcinol sulphate, the acid quinin quinol sulphate, the acid quinin pyrogallol sulphate, and the acid cinchonidin pyrogallol sulphate. The author further prepared and describes the normal quinin orcinol sulphate, quinin catechol sulphate, cinchonidin quinol sulphate, as well as the quinin resorcinol, quinin catechol, and quinin pyrogallol hydrochlorides. They are beautifully crystallized compounds and some of them excellent febrifuges.

YOHIMBE, QUEBRACHO, PSEUDOCINCHONA AFRICANA, ANGOSTURA, ALSTONIA, GEISSOSPERMUM

The barks of several trees belonging to the Rubiaceæ, Apocynaceæ and Rutaceæ are credited with febrifugal, tonic, and aphrodisiac proper-

ties. The drugs contain alkaloids possessing properties which in some instances are quite similar to each other, but as yet they have not been classified chemically. To avoid confusion, the data have been assembled under one heading, and placed next to Cinchona. Some of the drugs resemble Cinchona in appearance, and the alkaloids derived therefrom have similar physiological properties, though their chemical reactions are often more like those of the Nux Vomica bases.

The botanical identity of the plants from which the drugs are derived is not conclusive in every case, neither is the identity of the bases, as certain of the latter bear a close relation to each other and are perhaps isomeric or even identical.

These drugs are employed as bitter tonics, nerve tonics, and aphrodisiacs, and will be found in small amounts in alcoholic liquids recommended for recuperative and restorative purposes, often in combination with Turnera aphrodisiaca (Damiana).

ALKALOIDS OF YOHIMBE BARK

The bark of the Yohimbe or Yumbehoa tree, Corynanthe Yohimbe (Rubiaceæ), contains yohimbin and other bases as yet unstudied.

The especial microscopic characteristic of yohimbe bark is the structure of the secondary bark, which contains numerous yellowish-white bast fibers, regularly arranged, distinguishing yumbehoa bark from cinchona bark, otherwise similar. The powdered bark (fine and moderately fine only are considered) is characterised by (1) the numerous pore-free bast fibers, with complete absence of stone cells, (2) the presence of greatly thickened porous and almost pigment-free cork cells, (3) the brown-walled, almost starch-free parenchyma, together with reddish-brown lumps of coloring matter. Cinchona barks are distinguished by the appearance of their bast fibers; cinnamon bark by the color, presence of stone cells, and high starch content.

Yohimbin

This alkaloid, which seems to be the chief base of the Yohimbe group, has been the subject of considerable research, though as yet its constitution is undetermined. Its formula has not been definitely settled, but it appears to be either $C_{22}H_{28}N_2O_3$ or $C_{21}H_{26}N_2O_3$. The latter value is the same as that determined for corynanthin, the alkaloid of Pseudocinchona africana, and quebrachin. The latest researches indicate that corynanthin is isomeric with yohimbin and dextro-quebrachin.

When yohimbin is heated two hours with alcoholic potash, a methyl group is split off and the potassium salt of an acid remains in solution, which crystallizes from water in glassy prisms. This body is called nor-yohimbin or yohimboaic acid and forms salts with both bases and acids.

Yohimbin is not simply a methyl ester of yohimboaic acid, esterification with different alcohols shows that two alkyl groups are taken up and one molecule of water is split off.

Corynanthin is also a methyl derivative, and on saponification yields an acid having the same composition as yohimboaic acid.

Yohimbin crystallizes in the dark from absolute alcohol in anhydrous white needles melting at 247–248°. It is dextrorotatory, readily soluble in alcohol, ether, and chloroform, slightly in petroleum ether, benzol, and water. Its salts with hydrochloric and nitric acids are used in medicine, the latter being but sparingly soluble in water.

Yohimbin residues give two reactions which deserve special consideration on account of their resemblance to those of strychnin, and which might lead to confusion and possibly erroneous conclusions if the analyst has but a small quantity of material at his disposal. On adding sulphuric acid to a residue, a yellow color is obtained, which on adding potassium bichromate becomes purple, changing to blue, red, and finally green; if the quantity is considerable the first color is indigo-blue, changing rapidly to olive-green. Nitric acid gives a yellow solution, which becomes orange on evaporation; this residue treated with alcoholic potash yields a purple color momentarily, then chocolate and on warming almost black; as the last portions of alcohol evaporate there is an odor of orange-flower. Yohimbin residues do not have the intense bitter taste that is characteristic of strychnin, and they are readily distinguished by the microscopic forms of the salts formed with gold chloride and other reagents used in the identification of strychnin.

A solution of yohimbin in concentrated sulphuric acid gives an intense orange with calcium hypochlorite. Formaldehyde-sulphuric gives a dark brown color.

Yohimbin gives precipitates with most of the alkaloid precipitants, most of the compounds are amorphous, including those with gold and platinic chloride. Chromic acid precipitates a mass of fine yellow crystals soluble in ammonia. Picric acid throws down yellow microscopic crystals which soon agglomerate and stick to the sides of the container. An alcoholic solution gives a white precipitate with bromine water. The precipitate obtained with mercuric chloride is crystalline and dissolves in water when the solution is diluted. Nessler's reagent gives a white amorphous precipitate and reduction takes place with ammoniacal silver nitrate.

Yohimbin hydrochloride is an anesthetic, but there is no likelihood of confusing it with cocain hydrochloride, after precipitating the alkaloid and subjecting it to the proper tests for identification.

The alkaloidal residue from yohimbe bark probably contains one or more bases in addition to yohimbin.

QUEBRACHO ALKALOIDS

The bark of Aspidosperma Quebracho-blanco (Apocynaceæ) contains aspidospermin, aspidospermatin, aspidosamin, quebrachin, hydro-quebrachin, and quebrachamin. The drug is not of common occurrence in medicine, though the extract is used extensively in tanning, and the composition and properties of the bases have been subjected to but little research. Quebrachin probably occurs in the racemic, lævo, and dextro forms, the latter being apparently identical with yohimbin.

The reactions of the bases may be summarized as follows:

Aspidospermin with sulphuric acid and lead peroxide gives a brown color changing to purple-red. When boiled with perchloric acid an intense red color results, the reaction probably depending on the presence in the acid of impurities having oxidizing power. Platinic chloride gives a blue precipitate which becomes violet on boiling with excess of the reagent. Potassium chromate produces a yellow precipitate which turns green on exposure to air.

Hydro-quebrachin gives a yellow color with sulphuric acid, and the same reaction with perchloric acid as aspidospermin. The chloroplatinate is yellow and dissolves in boiling hydrochloric acid with a brown red color, depositing a blue precipitate on standing.

Quebrachin gives a bluish solution with sulphuric acid, turning blue and brown with bichromate. With perchloric acid the color is yellow.

Quebrachamin gives a violet color with sulphuric acid and bichromate and a yellow to yellowish-red with perchloric acid.

Aspidospermatin gives with perchloric acid the same color as aspidospermin, but the precipitate with platinic chloride is yellow.

Aspidosamin gives a brown color with sulphuric acid, turning blue with bichromate, and a fuchsin red color with perchloric acid.

ALKALOID FROM PSEUDOCINCHONA AFRICANA

Chevalier in 1897 called attention to a bark used for febrifugal purposes by the natives on the Ivory Coast. Its botanical identity was unknown, but from its resemblance to Cinchona he gave it the name Pseudocinchona africana. Further study showed that it contained at least two alkaloids, one of which was crystalline and is probably isomeric with yohimbin, and the other amorphous. The former has been called corynanthin. On demethylation it yields an acid-like body apparently identical with yohimboaic acid, and in other respects it bears a close relationship to yohimbin. It crystallizes from absolute alcohol in colorless hexagonal plates, and from 60 per cent alcohol in elongated spangles with water of crystallization. It melts 241–242°, has $[a]_D$–125° at 23° with the composition $C_{21}H_{26}N_2O_3$, which makes it isomeric with dextro-quebrachin.

It is insoluble in petroleum ether, water and alkalies, but dissolves with greater or less facility in the organic solvents. It gives a blue color with sulphuric acid and bichromate, but its color tests have not been thoroughly studied. The characteristics of the bark from which it is derived have not been authentically reported.

THE ANGOSTURA ALKALOIDS

The bark of Cusparia officinalis, syn. C. trifoliata contains several alkaloids which have been studied by Tröger and others. The isolated bases have never been employed for medicinal purposes, but an extract of the bark has a limited use as a tonic and febrifuge and will be found occasionally as an ingredient of bitters and restoratives.

Tröger [1] mentions five bases occurring in the drug: galipoidin, melting 231°; cusparidin, melting 79°; galipidin, melting 111°; galipin, melting 115°; and cusparin, melting 89–90°. He concludes that galipin and galipidin are dihydro compounds of cusparin and cusparidin respectively. In a previous article [2] he describes cusparein, melting 55–56°, and angosturin, melting 231–233°. Later [3] he says that, besides certain oily bases, the extract of angostura bark contains only cusparin, galipin, and galipidin. Galipin was separated from cusparin by the difference in the solubility of the oxalates, that of galipin being readily soluble in water and crystallizing only at considerable concentration, cusparin oxalate being soluble only in a considerable excess of boiling water.

Galipin on oxidation with permanganate yields veratric and methoxyquinolincarboxylic acids.

The alkaloidal residue when dissolved in sulphuric acid and treated with a crystal of permanganate gives a reaction resembling that of strychnin.

ALKALOIDS OF THE ALSTONIA BARKS

Alstonia constricta (Apocynaceæ) of Queensland and New South Wales and A. scholaris, known as Dita bark of the Philippines, have been used in dysentery and intermittent fevers.

The bases of the former, alstonin, melting about 195°, and porphyrin, melting 97°, show a blue fluorescence in acid solution and might be mistaken for quinin.

Hesse examined the Dita bark and found three bases, ditamin, echitamin, and echitenin. The second is a strong base and resembles ammonia in its chemical characters. Hesse considers the compound given by echitamin with one molecule of water as the hydroxide of a strong basic radicle,

[1] Arch. Pharm., 240, 174. [2] Apoth. Zeit., 25, 957, 969, 977, 988.
[3] Arch. Pharm., 250, 494.

echitammonium. The solutions are so strongly basic that they precipitate the hydroxides of copper, iron, aluminum, and lead, and decompose sodium and potassium chlorides, liberating the corresponding hydroxides.

ALKALOIDS OF GEISSOSPERMUM

The following bases have been isolated from the bark of Geissospermum vellosi (Apocynaceæ), pereirin, melting 124°, geissospermin, and vellosin. The melting-point of geissospermin has been reported as 160° and as 189°, consequently the chemistry of this group is somewhat confusing. Under the name Pao-pereira this bark is used in Brazil as a febrifuge.

With the possible exception of yohimbin, the known reactions of the bases described under this group of drugs are, from an analytical standpoint, very meager and unsatisfactory, and capable of misinterpretation. In forensic work the advantage is all on the side of the chemist who is working for the party that knows the ingredients of the mixture in question, and he can of course plan his tests and interpret his reactions accordingly. With the chemist who takes the product as an unknown mixture the problem is entirely different, and as these preparations usually contain but a meager quantity of the drug, by the time he has come to differentiate between the several possible bases, he will find that his material is exhausted. To the analyst who finds himself in this position a few words of caution are necessary; the first is not to confuse those bases with strychnin and the second is to refrain from stating positively the source of the alkaloids found unless he has worked with known specimens side by side with the sample under investigation and is prepared to meet all possible criticisms from his adversaries. It is a simple matter to identify strychnin, as it yields several well-defined crystalline salts with alkaloidal precipitations, all of which can be easily identified under the microscope, while the precipitates given by the bases herein described are mostly amorphous. If strychnin occurs with these bases it is more than possible that the analyst will miss the latter and come in for a round of undeserved criticism and sarcasm from the opposition when the case is summarized.

CHAPTER VII

ALKALOIDS DERIVED FROM ISOQUINOLIN

THE OPIUM ALKALOIDS AND THEIR DERIVATIVES

Morphin, $C_{17}H_{19}NO_3$
Codein, $C_{18}H_{21}NO_3$
Pseudomorphin, $(C_{17}H_{18}NO_3)_2$
Thebain, $C_{19}H_{21}NO_3$
Papaverin, $C_{20}H_{21}NO_4$
Codamin, $C_{20}H_{25}NO_4$
Laudanin, $C_{20}H_{25}NO_4$
Laudanidin, $C_{20}H_{25}NO_4$
Laudanosin, $C_{21}H_{27}NO_4$
Tritopin, $(C_{21}H_{27}NO_3)_2O$
Meconidin, $C_{21}H_{23}NO_4$
Lanthopin, $C_{23}H_{25}NO_4$
Protopin, $C_{20}H_{19}NO_5$
Cryptopin, $C_{21}H_{23}NO_5$
Papaveramin, $C_{21}H_{21}NO_5$
Narcotin, $C_{22}H_{23}NO_7$
Gnoscopin, $C_{22}H_{23}NO_7$ stereoisomer
Oxynarcotin, $C_{22}H_{23}NO_8$
Hydrocotarnin, $C_{12}H_{15}NO_3$
Xanthalin, $C_{20}H_{19}NO_5$

The average relative proportions of some of these bases in the drug are approximately as follows:

	Per Cent		Per Cent
Morphin	9	Pseudomorphin	0.02
Narcotin	5	Laudanin	0.01
Papaverin	0.8	Lanthopin	0.006
Thebain	0.4	Protopin	0.003
Codein	0.3	Codamin	0.002
Narcein	0.2	Tritopin	0.0015
Cryptopin	0.08	Laudanosin	0.0008

OPIUM

The opium used in the manufacture of morphin and its accompanying alkaloids and for pharmaceutical preparations comes almost exclusively from Turkey and Asia Minor. It is the exuded juice of the black poppy (Papaver somniferum), which is gathered in a partially dry, gummy mass and sent into the trade in cakes of from 1 to 4 lbs. These cakes are usually wrapped with poppy or dock leaves and packed in cases with layers of dock capsules. The customs officials become very expert in the sampling of opium by the eye alone, and can tell by simply cutting into a cake whether it contains excessive moisture or extraneous substances, and is

of high or low grade. It is regarded as inferior if it is blackish in color, has a weak or empyreumatic odor, a sweet or slightly nauseous and bitter taste, a soft, viscid, or greasy consistency, a dull fracture, or an irregular appearance from the admixture of foreign substances. In the case of good opium, the lumps are usually hard on the outside, but still soft within, the internal color being light brown, and the interior containing but few, if any, dock capsules. On cutting open and tearing apart the lump, numerous minute shiny tears will sometimes be observed. The odor is pleasant and characteristic.

Opium is adulterated with chunks of lead, stones, bullets, sand, clay, and other weight-producing substances, sugar, starch, tragacanth, fruit pulp, extract of licorice, poppy, and other plants and vegetable substances of a resinous or saccharin nature; and if it has been kept under damp conditions it will have become moldy. The composition of good opium is about as follows:

	Per Cent
Moisture	8–30 averaging 20
Ash	4–8
Gum and soluble substances other than alkaloids	40–60
Morphin	6–15
Narcotin	4–8
Other alkaloids	0.5–2
Meconic acid	3–8
Resins	5–10
Fat	1– 4

and it should yield 55–60 per cent of extractive matter to cold water based on the dry product.

Smoking opium is no longer imported legitimately, but it is probably illegally made in this country, and smuggled in to a limited extent. The product is an aqueous extract of opium evaporated down to the consistency of a thick molasses, and is similar in every way to the old U. S. P. extract of opium. Smoking opium from China averages about 6.5 per cent morphin, while that made from Smyrna gum runs from 16 to 18 per cent.

The sampling of opium requires considerable care, as the determination of the value or condition of the entire lot or case is often dependent on the assay. Squibb recommends that every fifth lump should be taken, except the very small ones, and then every tenth lump of these be separated, a cone-shaped piece cut from each, the apex of the cone being near the center of the lump. A narrow strip is then cut from the side of each cone, the strips collected together in a cone, and this sample used for the determination of the moisture and morphin. The methods of assaying opium for its morphin content are described in the chapter on Drug Assays.

Kerbosch [1] has made an interesting investigation of the occurrence and distribution of certain of the alkaloids in the poppy plant. The seeds contain traces of narcotin and an amorphous alkaloid and three days after germination notable quantities of narcotin are present, soon followed respectively by codein, morphin, papaverin, and thebain. The flowering plant up to the time of ripening contains narcotin, papaverin, codein, and morphin in all its organs with the exception of the hairs. The latex varies in composition in different parts of the plant.

Morphin, codein, meconidin, codamin, laudanin, laudanidin, laudanosin, protopin, and cryptopin are all strong bases and narcotic or tetanic in their action, the others are weak bases and have little or no poisonous activity. They are present in the drug in acid combination to a large extent, the acid radicles being chiefly meconic and sulphuric. The drug analyst will seldom be concerned with the identification or determination of the entire list. Morphin, codein, thebain, narcotin, narcein, and papaverin are the only individuals with which familiarity is necessary, and in addition to these bases meconic acid is of moment, as its identification is an important factor in establishing the presence of opium in a preparation. The recognition of this group is easy, either alone or in mixtures.

In medicinal preparations one will find that morphin, opium extract, and codein, and in addition to these some of the derivatives, heroin, apomorphin, and dionin, are used to a considerable extent. They are all useful for diminishing pain and inhibiting secretions except that of the skin, and are generally narcotic and will be found in cough mixtures, lozenges, and soothing syrups, diarrhea mixtures, neuralgia remedies, anodynes, coryza mixtures, consumption remedies, habit cures, and in a variety of imported foreign drug products, notably Chinese remedies. Several products having a household reputation contain these bases, among which may be mentioned Dover's powder, paregoric, laudanum, sun cholera mixture, brown mixture, white pine cough syrup, and chlorodyne.

Considering the products separately, opium will be found alone in laudanum or tincture of opium, fluid opium, wine of opium, and some elixirs of a similar nature having different trade-marked names, " cures " recommended for the opium habit, and in pills. It occurs in combination with camphor, oil of anise, and glycerin in paregoric, or camphorated tincture of opium, this combination being in some respects similar to the well-known proprietary " Bateman's Pectoral Drops," which also has been made up to include catechu. It is a constituent of ammoniated tincture of opium, similar to paregoric except that camphor is replaced by dilute ammonia. Black drop is essentially an acetic acid solution of the constituents of opium. It is combined with potassium carbonate, oil of sassafras, and molasses in a type of mixtures resembling Godfrey's

[1] Arch. Pharm., 1910, 248–336.

Cordial; with magnesium carbonate, anise, nutmeg, peppermint, and castor oil in products of the Dalby's Carminative type; and in tinctures combined with ipecac. Opium in powdered form is mixed with powdered ipecac in the well-known Dover's powders, and with pepper, ginger, and caraway in compound opium powder. The different pill and tablet combinations in which opium occurs are numerous, some of the more common being with ipecac and mercury mass; asafetida and ammonium carbonate; calomel, camphor, and lead acetate, or in place of the latter tannin or hyoscyamus; guaiac and mercuric chloride; mercurous iodide, lead acetate, phosphorus, Digitalis with and without quinin or ipecac; ipecac, quinin and belladonna; licorice, benzoic acid, camphor, tartar emetic and anise in brown mixture; calomel and ipecac; copper sulphate, ipecac, and squills; potassium iodide, potassium arsenite, Lobelia, and belladonna in asthmatic remedies; bismuth subnitrate and carbolic acid; quinin, ammonium chloride, camphor, belladonna, and aconite; Krameria, bismuth subnitrate, and licorice; Hyoscyamus, Hamamelis, tannin, thymol, helonias, salicylic acid, boric acid, alum, and eucalyptol in leucorrhea mixtures; white pine, wild cherry, squill, senega, ipecac, Sanguinaria, potassium nitrate, and methyl salicylate; capsicum, rhubarb, camphor, and oil peppermint in sun cholera mixture; terpin hydrate, guaiac, wild cherry, and belladonna; aloin, Capsicum, aconite, quinin, ipecac, and calomel in cold remedies; and quinin, ammonium chloride, camphor, belladonna and aconite. This list does not by any means cover the field of combinations, new formulas are constantly being introduced, but it will show in a general way the type of mixtures on the market, and the class of substances with which opium is combined. Opium should be looked for also in suppositories, in admixture with tannin, menthol, camphor, and boric acid, and in ointments recommended as local applications for croup and pneumonia where it occurs with quinin, camphor, phenol, and turpentine.

Morphin in the form of sulphate, hydrochloride, nitrate, meconate, tartrate, phthalate, and valerianate, occurs alone in pills and tablets and will sometimes be found in snuff powders and as a remedy for the morphin habit. It also occurs as the oleate. Morphin sulphate and atropin sulphate in various proportions are combined in hydopermic tablets to a large extent; and it is used in conjunction with cocain in dental tablets, and to a limited amount with strychnin. It is also present in place of opium in some of the mixtures mentioned above; chlorodyne mixture contains morphin hydrochloride, nitroglycerin, Cannabis, Hyoscyamus, Capsicum and peppermint; morphin bromide compound contains morphin and scopolamin ("hyoscin") hydrobromates with monobromated camphor; uterine astringent and antiseptic tablets consist of alum, zinc sulphate, tannin, boric acid, morphin sulphate and extract Hydrastis; medicated lozenges contain ipecac and morphin sometimes with other ingredi-

ents; white pine compound, a liquid cough remedy contains morphin acetate, sassafras, Sanguinaria, spikenard, wild cherry, white pine bark and balsam of poplar buds and sometimes chloroform and tar are used; morphin sulphate will be found in combination with laxative drugs in liquid preparations sold as cures for the morphin habit.

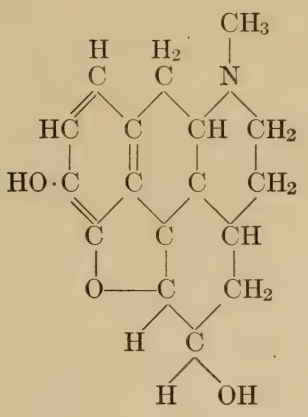
Codein has a much more restricted use than opium or morphin, but the combinations in which it does occur are sold to a large extent. It occurs alone in pills and tablets and in hypodermic tablets, especially as the phosphate and is often combined with acetanilid, caffein, bromides and sodium salicylate; with antipyrin, spartein, strophanthus and caffein; and with colchicin and sodium salicylate. In the liquid form it is mixed with acetanilid, caffein, and bromides, and often replaces morphin in cough mixtures of the white-pine type. It is said to have been used to some extent in confectionery sold for throat troubles.

Heroin is employed as a substitute for morphin in cough mixtures and is also mixed with terpin hydrate in elixirs, and sold alone in tablet triturates and hypodermic tablets.

Apomorphin is employed chiefly in the form of hypodermic tablets.

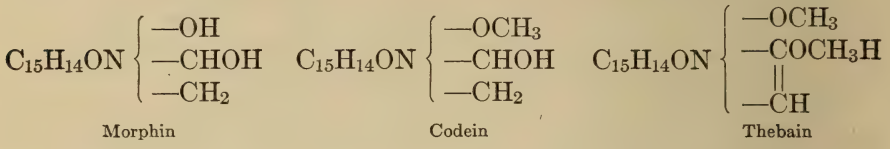
The other alkaloids of opium or their derivatives are either used by themselves or have no commercial use other than in their extract form.

Morphin



Morphin crystallizes out of alcohol in prisms containing one molecule of water. It is lævorotatory, slightly soluble in water, ether, chloroform, and benzol, but readily soluble in alcohol, alcohol-chloroform mixture, amyl alcohol, acids, and alkalies. Its water of hydration is given off at 100° and the alkaloid melts at 254° C. when heated rapidly. When heated slowly it begins to melt at 247° with decomposition. Morphin with its water of hydration melts at about 230° C.

It is a strong tertiary base and also a monatomic phenol, dissolving in alkalies to form salts with one atom of the metal which are decomposed by carbon dioxide or ammonia. This property of forming salts with alkalies is used to good advantage in separating morphin from other alkaloids. It forms diacetyl and dibenzoyl derivatives. On strong oxidation with dilute nitric acid it gives a dibasic acid, $C_{10}H_9NO_9$, and this on further treatment with fuming nitric acid is converted into picric acid. On methylation it is changed to codein, the group being introduced on the phenolic hydroxyl. Thebain may be considered as oxymethyl codein and the relationship of these three bodies may be represented as follows:



Morphin Codein Thebain

When fused with potassium hydroxide morphin gives protocatechuic acid. Acids, alkalies, and zinc chloride remove a molecule of water and convert it into apomorphin, which is soluble in ether and chloroform.

Morphin is readily oxidized even by gold and silver salts, and iodic acid. On oxidation by weak oxidizing agents, pseudomorphin is formed according to the reaction,

$$2C_{17}H_{19}NO_3+O=(C_{17}H_{18}NO_3)_2+H_2O$$

It is precipitated by the usual alkaloidal precipitants, but not by potassium chromate or ferrocyanide, and gives some interesting color tests both in aqueous solution and as a dry residue. A neutral aqueous solution gives a deep blue-green color with ferric chloride, changed to green with excess of the reagent and disappearing on the addition of acids or alcohol or on heating. Pseudomorphin gives a blue color and codamin a dark green. An aqueous solution reduces iodic acid with liberation of iodin, which will dissolve in carbon bisulphate or chloroform with a violet color. Morphin will reduce potassium ferricyanide, being itself oxidized to pseudomorphin, and if an aqueous solution slightly acidified is added to a solution of potassium ferricyanide and ferric chloride a blue precipitate or coloration will be produced due to the formation of Prussian blue.

Iodic acid followed by ammonia gives a mahogany color which is a positive test, while the simple reduction is not necessarily characteristic of morphin. Iodic acid is reduced by extractive matter from animal tissues, some medicinal drugs and inorganic compounds. The iodic acid ammonia test, however, is distinctive according to Peterson and Haines;

they report its application to numerous extracts from putrefied animal matter of various kinds, and in no case was a fallacious indication obtained.

The iodic acid test may be applied directly to a dry residue on a smooth porcelain surface. A drop of the reagent is added to a small quantity of the suspected residue and after standing ten minutes, any iodin is washed off by floating over it a drop or two of chloroform, repeating until the spot is colorless. When dry a drop or two of 10 per cent ammonia water is added, when a mahogany color indicates morphin. The decanted chloroform is then evaporated and tested with a little starch paste, which will turn blue if free iodin is present.

Strong nitric acid added to solid morphin turns it a deep red or orange-red color, the crystals dissolving to an orange-red solution, gradually fading on standing. A drop of stannous chloride added to the red solution produces no change, differing from the brucin nitric acid color which thereby is changed to purple. Strong sulphuric acid gives only a faint pink color with morphin when both substances are pure, and the color soon fades. If a solution in concentrated sulphuric acid is warmed to 100° C. and then treated with concentrated nitric acid, a chlorate, chlorin water or sodium hypochlorite, a blue or purplish color is obtained, passing to deep red and gradually fading. This is known as Husemann's test and is very delicate. Chloral or bromal added to a solution of morphin in strong sulphuric acid, produce a deep purple color and Froehde's reagent a deep purple fading to slate. Ammonium persulphate in sulphuric acid gives pale orange.

If morphin is treated with a little sugar, moistened with a drop of water and made into a paste and a drop of sulphuric acid is allowed to flow alongside the mixture, an intense purple color will develop at the point of contact, changing to violet and green to yellow

With bichromate and sulphuric acid a greenish color is produced and with vanadium-sulphuric acid, colors from yellow, passing to violet brown and slate are obtained.

A dilute solution of morphin treated with 1 mil each of 3 per cent hydrogen peroxide and dilute ammonia, followed by 1 drop of copper sulphate solution 1–4 per cent gives a color varying from rose to red. Denigès recommends this reaction in testing for morphin directly.

Apomorphin and oxymorphin react in a similar manner in syrups, but codein, thebain, papaverin, narcein, and narcotin give negative results.

Solutions of morphin give characteristic crystalline precipitates with iodin solution, palladous chloride, picrolonic acid and other reagents and a microscopical examination of the forms of these compounds is one of the most valuable means of identifying the base and distinguishing it from its allies.

If morphin is dissolved in hydrochloric acid, a little sulphuric acid added and the mixture evaporated on an oil-bath at a temperature of 100–120° a purple color appears on the edges, and after the volatile acid is all evaporated a red color remains. On dissolving again in hydrochloric acid and neutralizing with sodium bicarbonate a violet color is obtained. If hydriodic acid is added the color changes to green and on shaking with ether, the solvent becomes purple.

When morphin is mixed with hydrastin and treated with a little concentrated sulphuric acid, a faint pink color is given which soon fades, and then very gradually a reddish purple shade develops, which after some time changes to green. If a crystal of bichromate is added as soon as the mixed alkaloids have dissolved in the acid, a slate color appears, changing to indigo blue and then to a deep purple which is quite permanent for some time and then gradually passes to brown. This test has become known as the Lloyd reaction, and might under some circumstances be mistaken for a strychnin test. However, neither morphin nor hydrastin give a purple color when evaporated with nitric acid and treated with alcoholic potash, which happens with strychnin. It is stated that the veratrum alkaloids when mixed with hydrastin and treated with sulphuric acid will give a violet color.

Morphin is not removed from acid aqueous solution by solvents, and from alkaline liquids is extracted only by amyl alcohol or an alcohol-chloroform mixture. If the solution is made alkaline with ammonia under ordinary conditions minute amounts will be taken up by ether and chloroform, but in the presence of sodium or potassium hydroxide it is insoluble, and may thus be separated from most of the other alkaloids. It has been shown that an acid solution of morphin containing a little alcohol, saturated with sodium chloride and rendered alkaline with a slight excess of ammonia, will give up its morphin by shaking six to ten times with chloroform. It is well known that alkaloids in the freshly precipitated, or so called " nascent " condition, are far more readily soluble than when they have been allowed to crystallize. Morphin when dissolved in chloroform may be removed from this solvent by solutions of the caustic alkalies.

Alkyl derivatives of morphin are easily produced by dissolving the base in alcohol and heating for two hours under a reflux condenser in the presence of the alkyl sulphate of potassium or sodium.

Carbonic esters may be prepared by dissolving morphin in alcohol, adding alcoholic alkali and a slight excess of the alkyl chloro-carbonate. The reaction takes place at once with rise of temperature. The mixture is then neutrallized with sulphuric acid, the alcohol distilled off, the residue dissolved in water and the ester of morphin carbonic acid liberated by alkali, and dissolved out in benzol.

Of the salts of morphin the acetate, hydrochloride and sulphate will be encountered most frequently. Morphin acetate contains three molecules of water and occurs as a white or yellowish powder, very soluble in water and partially decomposed on boiling or evaporating. Morphin hydrochloride contains three molecules of water which are lost at 100° C. The crystalline salt is in white needles or minute cubes. The sulphate containing five molecules of water is probably the compound which has the widest use. It crystallizes in bundles of silky needles, and as found on the market is usually in small cubes. It loses $3H_2O$ at 100° and the remainder at 110°. This is the form used to a large extent in making hypodermic tablets; for sale in $\frac{1}{8}$-ounce vials to those addicted to the habit; for mixing with sugar and other inert substances in snuffs; and for cough mixtures, and various pill and tablet formulas. It has been observed that commercial morphin sulphate sometimes contains an appreciable quantity of codein. This is due to imperfect methods of manufacture and is not an intentional adulteration.

There are many other salts of morphin on the market but their use is comparatively limited.

Morphinmethylbromide

This product, known also as morphosan, closely resembles morphin in some of its properties. It forms white needle-shaped crystals, readily soluble in water, slightly in alcohol, and almost insoluble in ether and chloroform. It becomes anhydrous at 100–110°, and melts with decomposition at 264–265°. Its solutions give a blue color with ferric chloride and a blue precipitate with ferric chloride and potassium ferricyanide. It dissolves in sulphuric acid with a yellow color, and in Froehde's reagent with a violet color soon changing to dark green. Nitric acid produces a blood-red color, and formaldehyde sulphuric a red-violet changing to blackish green. Its solution is not precipitated by ammonia and it gives a test for bromine on decomposing with nitric acid in presence of silver nitrate.

Codein. $C_{17}H_{18}(CH_3)NO_3$

Codein or methyl morphin occurs in white prismatic crystals. It crystallizes from water with one molecule of the solvent and melts under boiling water to an oily liquid. Anhydrous codein melts at 155°. It is fairly soluble in water, especially when hot, and also in ammoniacal solutions, the latter property distinguishing it from morphin and useful in separating it from that base. It is readily soluble in alcohol, chloroform, benzol, ether, and amyl alcohol. It is practically insoluble in petroleum

ether and only slightly soluble in fixed alkalies. Its solutions are alkaline in reaction and lævorotatory.

With dehydrating agents, codein either forms condensation products, or loses a molecule of water and is converted to apocodein, $C_{18}H_{19}NO_2$.

Codein resembles morphin in some of its color reactions, but is sharply distinguished from it in others, and in its solubility in the ordinary organic solvents. With sulphuric acid no color is produced but if a trace of arsenate, dilute nitric acid, or ferric chloride is present, a blue color is produced. With nitric acid a yellow color is obtained, the crystals assuming an orange color until dissolved. Formaldehyde-sulphuric acid gives a deep purple color so closely resembling the shade obtained with morphin that it cannot be used as a distinguishing test. Froehde's reagent produces no change at first, but a blue color gradually appears. Vanadium-sulphuric acid gives a green, and then gradually a blue color. Sulphuric acid containing ammonium selenite gives a green color; ammonium persulphate in sulphuric acid, orange.

Pure codein does not reduce iodic acid; its solution does not give a blue color with a solution of ferric chloride, nor a blue precipitate with the latter and potassium ferricyanide.

When dissolved in concentrated sulphuric acid and treated with a drop of 10 per cent sugar solution, a violet-red color appears which changes rapidly to deep red on heating over a water-bath.

Codein picrate, prepared by precipitation from hydrochloric acid solution and recrystallized from 10 per cent acetic acid, melts 195.5–196° C.

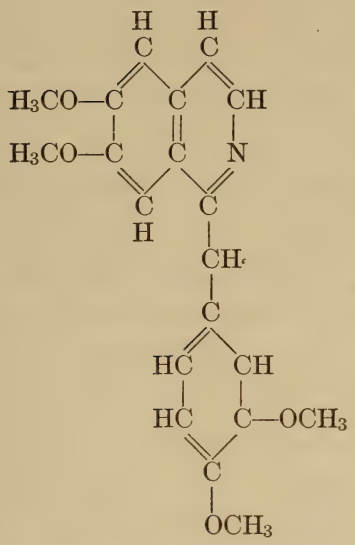
Codein may be prepared synthetically from morphin, and may be considered a methyl derivative.

Pseudomorphin

Pseudomorphin sometimes occurs in opium, and may be prepared by the mild oxidation of morphin. In composition it may be considered as a product resulting from the condensation of two molecules of morphin with the loss of two atoms of hydrogen. It crystallizes in leaflets containing $3H_2O$, which decompose without melting. It is soluble in alkalies and ammonia, but insoluble in water, acids, alcohol, or ether. It is a non-poisonous weak base. It contains four hydroxyl groups and gives a tetra-acetyl derivative.

Pseudomorphin will be of little concern to the drug analyst unless he becomes involved in a toxicological case where there is a question of its formation in the body as a condensation product of morphin. Its color reactions have been only imperfectly described. Hesse states that it gives a green color changing gradually to brown with sulphuric acid and sugar, and a blue to green with sulphuric acid containing a trace of iron.

Papaverin



The so-called papaverin group of the opium alkaloids includes most of the bases other than those previously described. They are all related to each other constitutionally and their structural groupings have, in some instances, been definitely established. Papaverin, narcotin, and narcein are the three most important and are the individuals with which the drug analyst may at times become concerned. They are all derivatives of isoquinolin, and their basic character is weak, standing thus in sharp contrast to morphin, codein, and thebain.

Papaverin crystallizes in prisms or needles, melting 146–147°. It is inactive to polarized light. It is insoluble in water and alkalies, but dissolves readily in hot alcohol, chloroform, benzol, and hot petroleum ether, and is somewhat soluble in ether. It is easily removed from an acidulated solution by chloroform and partially by ether. Narcotin is also removed from an acid solution by chloroform, and may be separated from papaverin by dissolving in oxalic acid and concentrating until the sparingly soluble acid oxalate of papaverin crystallizes out. Papaverin forms a very insoluble benzoate.

This base gives with strong acids and oxidizing agents some well-marked color tests which are distinct from the colors given by narcotin and narcein, though it may be stated at this point that variations in color given by the latter may be due to the impurities present of which papaveramin and cryptopin are of especial moment. It dissolves in concentrated sulphuric acid to a colorless solution, becoming violet on heating. Froehde's reagent gives a purple, gradually changing to blue; sulphuric

acid and bichromate purple, turning brown and then changing back to purple; formaldehyde-sulphuric acid purple changing to crimson; and ammonium vanadate in sulphuric acid purple, blue, green and finally deep blue. It dissolves in nitric acid to a yellow solution. Narcotin gives a purple color with formaldehyde-sulphuric acid which turns to slate and soon fades, but gives no purple tint with any of the other reagents above mentioned. Narcein gives no purple color with any of them. Ammonium persulphate in sulphuric gives yellow with papaverin.

On mixing papaverin ferricyanide with formaldehyde-sulphuric acid, a light-blue color is produced, soon changing to violet and finally green, the color then fading to brownish yellow. A similar change of colors results when papaverin and potassium ferricyanide are mixed in the dry state, and treated with formaldehyde-sulphuric acid. Warren [1], who first reported this reaction, subjected a number of alkaloids to this test and found that, with the exception of an uncertain base from Sanguinaria, none gave a reaction like papaverin. However, if selenious acid be used as the oxidizing agent, the initial color produced by the Sanguinaria base is an intense purple, while papaverin when thus treated gives a fugitive greenish blue which becomes deep blue. Warren found that a mixture of potassium permanganate and papaverin treated with formaldehyde-sulphuric acid gave a green color, almost instantly changing to blue, then deepening into an intense violet-blue which after some time becomes bluish green, then green and finally dirty brown.

Mullikin states that the pure base prepared from the oxalate which has been repeatedly crystallized gives no color reactions with concentrated sulphuric acid, Froehde's, Mandelin's or Erdmann's reagents, and that with formaldehyde-sulphuric acid, the color is a faint pink changing to brown. He claims that the color reactions given by commercial papaverin are due to the presence of cryptopin.

Papaverin gives precipitates with several of the alkaloidal precipitating agents, but in dilute solutions none with phospho-molybdic acid, and is not thrown down by potassium-cadmium iodide. An alcoholic solution of iodin added to an alcoholic solution of papaverin gives a crystalline precipitate on standing; this precipitate is decomposed by alkalies and ammonia. It forms a very sparingly soluble ferricyanide and acid oxalate. The picrate melts 179–181°, and the picrolonate 220° C.

When oxidized with permanganate, papaverin yields a large number of well-defined compounds, among them being a body to which the name of papaveraldin has been given. Its composition is $C_{20}H_{19}NO_5$, melting at 210°, and it differs from papaverin in possessing one more oxygen and two less hydrogen atoms. It is apparently identical with xanthalin. It reacts with hydroxylamin and phenylhydrazine, and when fused with

[1] J. Amer. Chem. Soc., 27, 1915, 2402.

alkalies is decomposed into veratric acid and dimethoxyisoquinolin. Another product of oxidation is papaveric acid, $C_{16}H_{13}NO_7$, melting 233°. It is a dibasic acid containing a ketone group and on fusion with alkalies is converted to protocatechuic acid. Veratric and protocatechuic acids are among the final products of the direct fusion of papaverin with caustic alkalies.

Hesse [1] has called attention to the fact that some of the samples of papaverin which he obtained had a percentage of carbon slightly above the normal even though he subjected them to repeated purification. The composition corresponded to $C_{21}H_{21}NO_4$, and the alkaloid appeared to be more soluble in cold alcohol than was pure papaverin. Hesse has given the substance the name pseudopapaverin and believes that in some seasons it predominates while in others the normal form is obtained only.

The complete synthesis of papaverin has been accomplished by Pictet and Gams.

Papaveramin

This alkaloid crystallizes in prisms melting at 128–129°; sightly soluble in water, alkalies, ether, and benzol, readily soluble in alcohol and chloroform. It is of interest especially as an impurity of papaverin, which it follows very closely in its solubilities and other properties, and is probably the constituent of crude papaverin which causes violet-blue color with concentrated sulphuric acid.

Xanthalin

This base is identical with papaveraldin, a product of the oxidation of papaverin with permanganate. It has been isolated from opium, though it is possible that it is formed from papaverin during the process of extraction. It is a crystalline powder, melting 208°, insoluble in water and alkalies, slightly soluble in alcohol and readily soluble in chloroform. Its salts have a yellow color.

Laudain, Laudanidin, Laudanosin, Tritopin and Codamin

These alkaloids are all closely related and are strong poisonous bases. The composition of laudanosin has been established as dextro-*n*-methyltetrahydropapaverin, laudanin is *n*-methyl-trimethylpaperverolin, and laudanidin is probably its lævo modification.

Laudanin crystallizes from alcohol or chloroform in prisms, inactive to polarized light, melting at 166°, readily soluble in alcohol and ether. It contains a phenolic hydroxyl and a neutral solution of its salts gives a green color with ferric chloride. With pure sulphuric acid it gives a

[1] J. prakt. Chem., 1903, 68, 190.

faint pink tint, deepening if a trace of iron is present and turning to violet on heating. Nitric acid produces an orange-red color.

Laudanin is not removed by chloroform from its solution in alkali hydroxides, but on adding ammonia the base is precipitated and may then be extracted. It forms a sparingly soluble hydriodide. When treated with methyl iodide in alkaline methyl alcohol, laudanin gives laudanin-methyl chloride and laudanin-methyl ester which is identical with *i*-laudanosin obtained from papaverin.

Laudanidin closely resembles the former alkaloid, but is lævorotatory and melts 177°. It may be separated from laudanin by means of its hydrochloride, which is readily soluble in water; the hydrochloride of laudanin separates out from hydrochloric acid solution, especially if sodium chloride is present to accelerate the precipitation. Its salts other than the hydrochloride closely resemble those of laudanin.

Laudanosin crystallizes in needles, melting at 89°, soluble in alcohol, ether, chloroform, and benzol, and insoluble in water and alkalies. It is dextrorotatory. It gives no color with ferric chloride, and with sulphuric acid alone and with oxidizing agents the reactions are similar to those given by laudanin. It gives a sparingly soluble hydriodide which serves as a very satisfactory means of separation. *N*-methyl-tetra-hydropapaverin, prepared synthetically, is identical in its chemical properties with laudanosin. It is a racemic body and may be separated into its constituents by quinic acid, the *l*-compound being much less soluble in alcohol; the *d*-body is identical with natural laudanosin.

Tritopin crystallizes in prisms from alcohol or in plates from ether, melting 182°. It is easily soluble in alkalies but is reprecipitated on adding excess of the reagent. It dissolves readily in chloroform and slightly in ether. Its color reactions with sulphuric acid are similar to those of laudanin.

Codamin

Codamin is a strong base, melting 121–126°, readily soluble in the ordinary solvents and alkalies and somewhat soluble in water. It gives a deep-green color with nitric acid and a greenish blue with sulphuric acid containing a trace of ferric chloride.

Both laudanin and laudanidin are isomeric with codamin.

Meconidin

Meconidin is a strong base which occurs as a brownish-yellow amorphous mass becoming liquid at about 58°. It is insoluble in water, but dissolves readily in alkalies and in the ordinary organic solvents. It is not removed from its solution in caustic alkalies by ether, but is shaken out of ammoniacal solutions with readiness.

Lanthopin

Lanthopin is another of the minor alkaloids of opium and a weak base, soluble in alkalies, chloroform, ether, benzol, and alcohol, melting about 200°. It gives a colorless solution with sulphuric acid, darkening on warming, and an orange-red solution with nitric acid. It gives no color reaction with ferric chloride.

Thebain

Thebain is a very poisonous, strong, tertiary base, which, as we have already observed, is closely related structurally to morphin and codein. It contains no hydroxyl group, and is unaffected by acetyl chloride or phosphorus pentachloride. It crystallizes from alcohol in leaflets, melting at 193°, and is readily soluble in alcohol, ether, chloroform, and benzol, almost insoluble in water and alkalies, and insoluble in petroleum ether. In the regular scheme of analysis it will occur in the fraction obtained by shaking out the ammoniacal solution with ether. When heated to 130° it sublimes in caffein-like needles. Narcotin, narcein, and papaverin do not sublime.

Thebain differs markedly from codein and morphin in its color reactions, giving a yellow with nitric acid and a red or reddish brown with sulphuric acid, Froehde's reagent, ammonium vanadate, and formaldehyde-sulphuric acid. It is precipitated from an aqueous solution of opium by sodium salicylate, which forms a very sparingly soluble thebain salicylate.

Dilute acids convert thebain into an amorphous base, thebanin, $C_{18}H_{19}NO_3$, which is sparingly soluble in hot alcohol, and insoluble in the other ordinary organic solvents.

The picrate, prepared as described under codein, melts 189–191° C.

Protopin

This is one of the minor alkaloids of opium, though it occurs in greater amounts in other drugs. It is of special interest from the fact that it is one of the few opium alkaloids that is not confined to that drug alone, but is quite widely distributed, being found in the root of Sanguinaria canadensis, Adlumia cirrhosa, Stylophorum diphyllum, Macleya cordata, and several species of Chelidonium and Corydalis. It is a strong narcotic base, crystallizing in needles from ether and chloroform, melting 202° (207° Mullikin), insoluble in water and fixed alkalies, slightly soluble in alcohol, ether, and benzol, but dissolving in ammonia and readily in chloroform. It gives a yellow to red color with sulphuric acid, and a deep violet with sulphuric acid containing iron oxide. It gives no color with ferric chloride. Mullikin states that the color with concentrated sulphuric acid is blue-violet changing to muddy violet with a green mar-

gin. Erdmann's reagent gives, according to the same authority, yellow, blue-violet, blue, green and yellow.

It forms an amorphous aurochloride melting 198° C.

Protopin appears to be identical with fumarin and macleyin.

Cryptopin

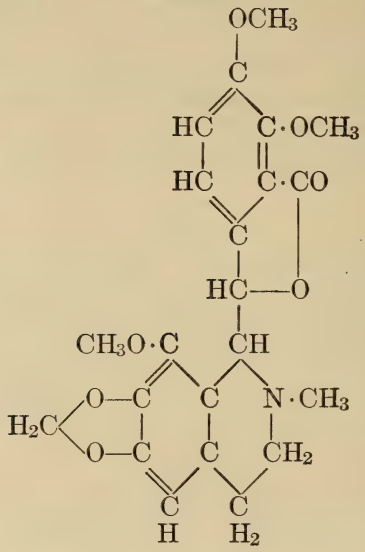
Cryptopin crystallizes from alcohol or ether in prisms, melting 213–218°. It is insoluble in water, alkalies, and ammonia, slightly so in ether, alcohol, and benzol, but dissolves readily in chloroform. It is a strong base and possesses hypnotic and mydriatic properties. With sulphuric acid it gives a violet color, changing to green and yellow, and if the acid contains iron oxide the color is deep violet. It occurs as an impurity in papaverin and is probably responsible for some of the color reactions attributed to its host.

Erdmann's reagent gives a violet pink, changing to gray and yellow; Froehde's reagent, violet changing to blue-green, green and after some time yellow; formaldehyde-sulphuric acid, violet changing to brown.

Salts of cryptopin, when dissolved in water, usually produce a gelatinous mass on cooling, and on standing the mass becomes crystalline. The picrate melts 215°.

Cryptopin is closely related to protopin. It contains two methoxyl groups.

Narcotin



Narcotin occurs in opium in varying amounts averaging about 5 per cent, and is one of the bases of this group, which may often prove of interest to the drug analyst. It is a weak base and probably exists in

the free state in the drug, from which it may be removed by simple extraction with ether. De-narcotized opium is a well-known article of commerce. Narcotin resembles papaverin and narcein by being extracted from acid solutions by chloroform; with papaverin it may be separated from narcein by precipitation with sodium acetate, and subsequently separated from papaverin by precipitating the latter with potassium ferricyanide.

It crystallizes from alcohol or ether in prisms melting 176°, insoluble in cold water and cold alkalies, slightly soluble in hot water and petroleum ether, somewhat soluble in alcohol and ether and readily soluble in chloroform and benzol. Its neutral solutions are lævorotatory and its acid solutions dextro.

Narcotin is precipitated by the general alkaloidal reagents. A solution of the alkaloid in dilute hydrochloric acid gives a yellow precipitate with bromin which dissolves on boiling. If bromin water is gradually added and boiled a rose color is produced and destroyed by excess of bromin. A solution of the alkaloid in very dilute hydrochloric acid gives a white precipitate with potassium thiocyanate.

If narcotin is heated with water at 140° or with sulphuric acid or barium hydroxide, it adds a molecule of water and is decomposed into opianic acid and hydrocotarnine. The opianic acid can then be recognized by the colorations produced with phenolic bodies. The test may be performed according to Labat [1] by dissolving .1 gram of the alkaloid in 0.5 mil of 10 per cent sulphuric acid and gently heating, after the addition of 2 mils of a 2 per cent solution of potassium permanganate, until the pink color has disappeared. The liquid is then diluted with alcohol until the opianic acid is approximately 1 per cent, and the solution used for the tests. On mixing 0.1 mil of this solution with 2 mils of concentrated sulphuric acid and 0.1 mil of the phenolic solution the following reactions are obtained: with 5 per cent alcoholic solution of gallic acid, a blue coloration rapidly appears changing to greenish brown; with a 5 per cent alcoholic solution of guaiacol or pyrocatechol gooseberry-red, changing to an intense blue when heated on the water-bath; with α-naphthol a gooseberry-red and with β-naphthol a wine red. Hydrastin will, of course, give the same reactions as it also is converted to opianic acid under similar conditions.

If 0.1 mil of an alcoholic solution of narcotin (1–100) is added to 2 mils of concentrated sulphuric acid, 0.1 mil of 5 per cent solution of gallic acid added and the tube heated in a water-bath, an intense emerald-green color is obtained, changing to bright blue. This reaction is also given by hydrastin and hydrastinin.

Zinc and hydrochloric acid, or sodium amalgam, reduce narcotin to meconin and hydrocotarnin.

[1] Bull. Soc. Chim., 1909, IV, 5, 743.

Narcotin dissolves in sulphuric acid, yielding a pale-yellow solution, pink on the edges, and a red color gradually develops. Nitric acid or sodium hypochlorite added to its solution in sulphuric acid produce a red or carmine, and ferric chloride a cherry red. It gives a deep yellow with concentrated nitric acid, a deep green with Froehde's reagent; a brick-red with vanadium-sulphuric acid; and a purple to slate, soon fading, with formaldehyde-sulphuric acid. Ammonium persulphate in sulphuric acid gives orange red.

Narcotin salts are not very stable, and water is usually sufficient to effect their decomposition. The hydrochloride and sulphate give clear solutions even when considerably diluted, but on adding sodium acetate to a solution of the hydrochloride the base is precipitated. The picrate melts 141° C.

Narcotin is converted to narcein by digesting for ten hours with excess of methyl iodide, removing the excess of the latter on the water-bath, dissolving the residue in alcohol and treating with chlorin water. A light-yellow precipitate is first formed, which soon dissolves; with excess of chlorin the precipitate is darker, and after standing a few hours becomes crystalline. The filtrate on evaporation yields a brownish gum, becoming crystalline narcotin methylchloride, which gives narcein by neutralizing with sodium hydroxide and passing a current of steam.

Gnoscopin

This alkaloid has been shown by Perkin and Robinson [1] to be racemic narcotin. It may be prepared from narcotin by heating with acetic acid to 130°, or by boiling cotarnin and meconin with potassium carbonate in alcohol. It melts at 228–233°, is insoluble in water and alkalies, slightly soluble in alcohol, and readily soluble in chloroform and benzol. It dissolves in sulphuric acid to a yellow solution, becoming red on the addition of nitric acid, the color being permanent. The picrate melts 200° C.

Oxynarcotin

This is a feeble base which occurs in crude narcotin. It is slightly soluble in alcohol and hot water and insoluble in the ordinary alkaloidal solvents.

Hydrocotarnin

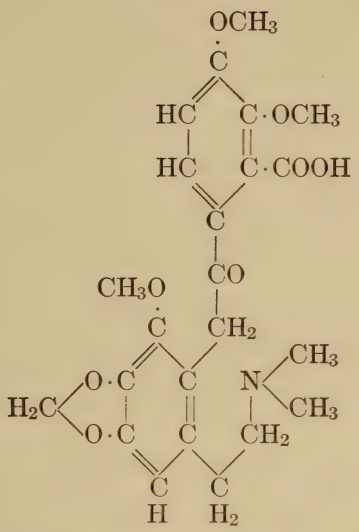
This alkaloid was found in opium by Hesse. It is formed by the decomposition of narcotin and crystallizes in prisms containing one-half molecule of water, melting at 55°. It is insoluble in water and alkalies but dissolves in organic solvents. It may be distilled with little decompo-

[1] Proc. Chem. Soc., 1910, 26, 46, 131.

sition at about 100° C. It is a tertiary base and a derivative of methyltetrahydroquinolin. By the action of sulphuric acid it forms a condensation product, hydrodicotarnin, $C_{24}H_{28}N_2O_6$.

Hydrocotarnin dissolves in concentrated sulphuric acid with a yellow color, changing to carmine, blue-violet, and violet on warming.

Narcein



Narcein has apparently the weakest basic properties of the opium alkaloids and has distinct acid properties. It contains a carboxyl and a carbonyl group, forms definite compounds with potassium and sodium hydroxide and reacts with hydroxylamine and phenyl hydrazine.

Narcein crystallizes from water or alcohol in prismatic needles containing 3 molecules of water, optically inactive, melting 170–171°. The water is all driven off on heating to 100° and the anhydrous base melts at 145°. As prepared commercially it is separated with difficulty from the acid radicle, even when precipitated in presence of free ammonia, and hence its melting-point is variable. It is slightly soluble in cold water and chloroform, readily soluble in hot water, alkalies, and alcohol, and insoluble in ether, benzol, and petroleum ether. It is partly removed from a cold acidulated solution by chloroform, but the extraction is not complete and it is carried along in the aqueous liquid through the shake-outs in alkaline solution until it is finally found in the alcohol-chloroform fraction with morphin.

Narcein gives no precipitate with Mayer's reagent, mercuric chloride, or potassium ferrocyanide; it is precipitated by gold and platinic chlorides, picric acid, tannin and by potassium bichromate on standing. With

iodin a brown precipitate is obtained, and on removing the excess of iodin by ammonia, the precipitate is found to be blue. Weak iodin solutions color narcein a dark blue; on dissolving in boiling water a colorless solution results from which violet or blue crystals separate on cooling. If iodin is strewn on a cold saturated solution of narcein, fine needle-like gray crystals form around the iodin. The picrate melts 127–128.5° and the platinochloride begins to darken at 190° and melts 198–199° C.

Narcein forms crystalline salts with caustic alkalies by heating the base at 60–70° with a 33 per cent solution of the alkali. The alkaloid is regenerated when the salts are treated with acids or carbon dioxide.

The color reactions of narcein are not especially characteristic; with sulphuric acid it gives a brown color, becoming yellow, green, and finally blue; Froehde's reagent gives greenish brown, vanadium sulphuric acid reddish brown; formaldehyde-sulphuric acid, brown, greenish on edges; nitric acid a fading yellow. When treated with sulphuric acid containing a trace of tannin a green color is produced, the same reaction being given by narcotin and hydrastin. When warmed with sulphuric acid containing a trace of resorcinol, a crimson to cherry-red color is produced, becoming blood-red on cooling and gradually fading to orange. Ammonium persulphate in sulphuric acid gives violet changing to blood-red and yellow.

A solution of narcein in very dilute hydrochloric acid gives a precipitate of white hair-like crystals becoming blue on standing, with a few drops of potassium-zinc iodide solution.

0.01 gram narcein in 5 mils of very dilute hydrochloric acid gives an orange-red coloration with 1 mil of chlorine water, followed by an excess of ammonia. Thebain under similar conditions gives a reddish-brown color.

Ethyl narcein hydrochloride is known as narcyl, and occurs in prismatic needles soluble in water and alcohol.

Apomorphin

This body was mentioned under the description of morphin as being one of its alteration products, differing from the parent substance by the elements of one molecule of water, and being the characteristic substance produced in performing Pellagri's test. It occurs on the market as the crystalline hydrochloride and is generally employed as an emetic, expectorant, or hypnotic in the form of syrups and hypodermatic tablets. It is a substance which is very prone to decompose and furthermore often contains impurities. It is seldom administered with other drugs.

The base itself, when freshly precipitated, is white and amorphous, but it soon turns green on exposure to light and air. It is readily soluble

in alcohol, ether, chloroform, and benzol; the solutions taking various shades of green, magenta, or violet. In the regular scheme of analysis, apomorphin will first make itself apparent when ammonia is added to the acid solution preparatory to shaking out with petroleum ether; at this juncture a green color appears, becoming more or less deep and intense, depending on the quantity of the base present; on shaking out with ether the solvent will acquire a magenta shade, due to the removal of some of the oxidation products. The same reaction will be obtained on shaking with either chloroform or benzol, the shades often varying from magenta to violet or purple.

These reactions are about all that is necessary to diagnose the presence of apomorphin. Pilocarpin gives oxidation products which dissolve in volatile solvents with bluish shades, but these oxidation products require for their production the assistance of some agent stronger than atmospheric oxygen, and hence are not formed in the ordinary procedure of analysis.

The color reactions given by apomorphin residues with the oxidizing agents used in the detection of the opium alkaloids are as follows: nitric acid gives at first a violet color soon changing to mahogany brown and later to orange; Froehde's reagent gives a deep blue, fading to slaty violet; vanadium-sulphuric acid a deep blue; formaldehyde-sulphuric acid a purple with a greenish-blue cast underneath, finally deep blue-black; bichromate and sulphuric acid deep green.

Apomorphin solutions, even when extremely dilute, give a green coloration when rendered faintly alkaline with potassium bicarbonaate. If a dilute solution is made alkaline with sodium hydroxide, a few drops of chloroform added and the mixture shaken, the chloroform will settle out with a blue color and the aqueous layer will be violet. With ferric chloride a rose-red color is obtained changing to violet and black. With a dilute solution of ferrous sulphate the solution becomes blue and then black, returning to blue on adding alcohol. Iodic acid gives the same coloration as is obtained with a solution of morphin.

The hydrochloride occurs in the amorphous state and in minute crystals, the latter form being the purest. The crystals should be kept tightly corked and away from the light and a freshly made solution should be colorless or with but a slight green color. Some commercial hydrochlorides have been found to contain varying amounts of beta-chloromorphide which may be detected by dissolving 0.1 gram in 10 mils of water, adding 5 mils of saturated sodium-carbonate solution, shaking with ether, washing the ether with 3 portions of water, and then evaporating the ether. The ether residue is then treated with 5 mils of concentrated nitric acid and .02 gram silver nitrate, and after standing a short time is heated on the steam-bath, water being added from time to time to keep

up the volume. If any appreciable amount of silver chloride is seen, the presence of the impurity is indicated.

If potassium ferricyanide is added to a dilute solution of apomorphin followed by benzol and shaking, the solvent will be colored an amethyst violet changing to violet red on shaking with sodium hydroxide.

The free base precipitated from hydrochloric acid solution by sodium bicarbonate, melts 160–170° with decomposition. The melting-point constant is not very reliable, because of the difficulty of obtaining a pure product free from oxidation products.

Apomorphin methyl bromide, $C_{17}H_{17}NO_2 \cdot CH_3Br$, known as euporphin, occurs in the form of colorless needles or scales, melting 180° C., and readily soluble in water and alcohol. It is used for the same purposes as apomorphin and its solutions seem to be more stable.

Apocodein

Apocodein, which is prepared from codein in an analogous way to apomorphin from morphin, is probably an indefinite mixture of basic derivatives of codein and morphin. It has a limited use as the hydrochloride, which is a yellowish to greenish-gray hygroscopic powder. The base gives a blood-red color with nitric acid; with Froehde's reagent a blue changing to brown and green to a purplish olive; with formaldehyde-sulphuric acid a brown to brownish purple, then black.

Eucodein

Codein methyl bromide occurs in colorless crystals, melting at 261°, readily soluble in water and slightly in alcohol. It is soluble in sulphuric acid with evolution of hydrobromic acid, gives a brown-violet to blackish-green color with formaldehyde-sulphuric acid, and a brown to dirty green with Froehde's reagent.

Heroin, Diacetyl morphin, $C_{21}H_{23}NO_5$

Heroin is probably the most widely used artificial derivative of morphin and is readily prepared from its parent base by heating with acetyl chloride or acetic anhydride. The diacetyl morphin is liberated by a mild alkali and extracted in the cold and may be crystallized out of alcohol. The free base melts 171–172°, is almost insoluble in water and petroleum ether, somewhat soluble in alcohol and ether, and readily soluble in chloroform and benzol. When heated in solution it is prone to decompose and in analytical work the manipulations must be done in the presence of ice. This factor must be considered in quantitative work when one is working with a product in which a stated amount of heroin has been declared. If a smaller quantity than that declared is found, it must not

be considered conclusive that the proper quantity was not originally present, but a further examination must be made for morphin.

It differs from morphin in being completely and easily removed from alkaline solutions by chloroform and in giving a pale-yellow color gradually turning green with nitric acid. It gives a brilliant crimson-purple color, soon fading, with Froehde's reagent, a permanent crimson-purple with formaldehyde-sulphuric acid; and a pale violet soon fading with vanadium-sulphuric acid. With hexamethylene tetramine in sulphuric acid a golden-yellow color is obtained, changing to saffron and finally to blue.

On heating with sulphuric acid and alcohol, ethyl acetate is formed, which becomes apparent by its odor.

Its neutral solutions do not liberate iodin from iodic acid, nor give a blue color with ferric chloride. It is precipitated by the ordinary alkaloidal reagents. The picrate, recrystallized from 50 per cent alcohol, melts 200–205° C.

Heroin is a cough sedative and antispasmodic, and is used in remedies for consumption, asthma, bronchitis, and similar ailments. The hydrochloride is a white crystalline powder readily soluble in water and alcohol.

Ethyl morphin, $C_{17}H_{18}(C_2H_5)NO_3$

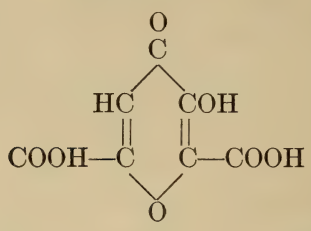
Ethyl morphin, the base of Dionin, which is its hydrochloride, is closely related to codein and resembles the latter in its properties. It is liberated from its acid solution by alkalies and may be completely removed from alkaline solution by ether and chloroform, but it is insoluble in petroleum ether. When heated to 110–115° it decomposes without melting. It gives a yellow color with nitric acid; a green to deep green and eventually a blue color with Froehde's reagent differing to some extent from codein in the first phase of this reaction; purple with formaldehyde-sulphuric acid; and green with vanadium-sulphuric acid. It is less soluble in ammonia than codein, a 10 per cent solution of the hydrochloride of the latter gives a precipitate on the addition of a few drops of ammonia soluble on the addition of 1 mil excess, while with a 10 per cent solution of dionin, the separated base does not go into solution until 5 mils of ammonia are added, and soon separates again on standing.

The hydrochloride, which is the form in which it is always found commercially, is a white crystalline powder, readily soluble in water and alcohol. A solution of the substance in water when added to ferric chloride containing a trace of potassium ferricyanide develops a blue-green color.

Benzyl Morphin, $C_{17}H_{18}NO_2OC_6H_5CH_2$

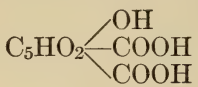
Benzyl morphin is the base of Peronin, the commercial name of its hydrochloride. It is liberated from its acid solutions by alkalies and under these conditions may be shaken out partly by petroleum ether and readily by ether. The residue gives a yellow color with nitric acid, a brown, violet, brownish green to slate with Froehde's reagent; an olive brown with vanadium-sulphuric acid; and a crimson, with a purplish shade gradually appearing with formaldehyde-sulphuric acid.

Meconic Acid

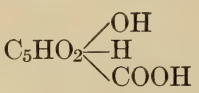


From an analytical standpoint, meconic acid is the most important of the non-basic constituents of opium for its identity serves to substantiate the presence of the drug. In the ordinary scheme of qualitative analysis, the acid will appear in the ether shake-out from acid solution and will be indicated by the deep-red color it gives when its aqueous solution is treated with ferric chloride. The deep-red color is not dispelled on warming with hydrochloric acid nor changed by gold chloride, it is, however, bleached by stannous chloride and restored by potassium nitrite. It may be purified by precipitating in aqueous solution with lead acetate, washing the precipitate, subjecting the latter to a stream of hydrogen sulphide in the presence of water and after filtering from the lead sulphide the pure acid may be shaken out with ether.

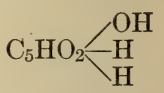
Meconic acid crystallizes in micaceous scales or rhombic prisms with 3 molecules of water. It loses its water of crystallization at 100° and at 120° is converted to comenic acid, $C_6H_4O_5$, with loss of CO_2, and on further heating yields pyromeconic acid with a further loss of CO_2.



Meconic Acid



Comenic Acid



Pyromeconic Acid

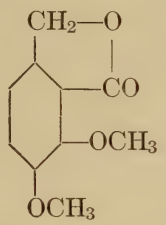
Comenic acid is insoluble in cold water and absolute alcohol and sparingly soluble in boiling water. Both this acid and pyromeconic acid give red colorations with ferric chloride.

Meconic acid is fairly soluble in cold and readily in hot water, and is rendered less soluble by the presence of hydrochloric acid. It is readily

soluble in alcohol and ether, and insoluble in chloroform. The solid acid gives a characteristic purple to deep blue color, gradually fading, with vanadium sulphuric acid. The microscopic appearance of its crystals from aqueous solution and of the precipitates with barium chloride, calcium chloride and potassium ferrocyanide are characteristic.

Meconin is often an impurity in the meconic acid extraction from opium and may be separated and identified by shaking the solution with benzol or chloroform which removes the meconin leaving the meconic acid in solution. On evaporating the solvent the meconin residue may be treated with concentrated sulphuric acid which will give a pale yellow color gradually changing to pale violet on standing. On adding a fragment of potassium nitrate to a solution of meconin in concentrated sulphuric acid, a yellow coloration is obtained, rapidly changing to scarlet.

Meconin is a neutral substance, somewhat soluble in boiling water, and ether, and dissolving readily in alcohol, chloroform, and benzol. It crystallizes in prisms which melt under water at 77°. The crystals melt in the air at 102–103°. It is a reduction product of opianic acid and is produced when narcotin is treated with zinc and hydrochloric acid. Its formula is



Qualitative and Quantitative Determination of the Opium Bases and Their Derivatives.—The alkaloids of this group are not difficult to detect and in the regular scheme of separation will appear in the several fractions where their identity will be indicated and from that point can be substantiated by applying the various reactions described for the specific individuals. As we have indicated in the preceding paragraphs, the number of individuals of interest from an analytical standpoint is limited to morphin, codein, narcotin, papaverin, thebain, narcein, and meconic acid among the naturally occurring substances; and to heroin, ethylmorphin, and apomorphin in the artificial group. In quantitative work the analyst will seldom be called upon to determine other than morphin, codein, heroin, and ethylmorphin. Morphin is, in one way, about the easiest alkaloid to separate from other bases as it is not removed from its solution in caustic alkalies by immiscible solvents, and from ammoniacal solutions with difficulty only with chloroform, and not with ether.

In qualitative work, an alcoholic extract of the dry sample or of an

evaporated liquid product should be concentrated to drive off the alcohol and then taken up with water and dilute sulphuric acid and subjected to the shaking-out scheme with immiscible solvents. Petroleum ether will remove nothing of interest of this group; ether will take out meconic acid, meconin, a little narcotin, and narcyl; chloroform will extract narcotin, papaverin, narcyl, and some of the narcein. The solution should then be rendered slightly alkaline with dilute potassium or sodium hydroxide and any green color noted which will at once indicate apomorphin; petroleum ether will take out some of the peronin if this substance is present; ether will remove apomorphin partly (both solvent and alkaline solution becoming colored, due to oxidation products), codein, ethylmorphin, thebain, apocodein, and laudanosin will be completely extracted, heroin, papaverin, and laudanin in part; following this shake-out chloroform will remove the rest of the apomorphin, heroin, laudanin, protopin, and a further quantity of papaverin if this has not been entirely removed in the previous fractions; morphin and narcein may then be shaken out by adding a little ammonium chloride and shaking out with chloroform-alcohol 2–1.

After evaporating the solvents in the separate fractions, portions of each residue should be examined in the following order: the ether fraction from acid solution will give evidence of meconic acid by the ferric chloride and vanadium-sulphuric acid test and this body can be separated from meconin and the latter detected as described under meconic acid; narcotin will be indicated by the tests with Froehde's reagent, vanadium-sulphuric acid, and formaldehyde-sulphuric acid. The chloroform residue from acid solution will give indication of narcein, narcotin, and papaverin by the color tests with sulphuric acid, Froehde's reagent, vanadium-sulphuric acid, formaldehyde-sulphuric acid, and nitric acid. In the petroleum ether residue from the alkaline solution peronin will be indicated by the tests with formaldehyde-sulphuric acid and Froehde's reagent. In the next residue, ether from alkaline solution, the greatest variety may occur; nitric acid will give green with heroin, yellow with codein, and violet to deep brown and finally orange with apomorphin; formaldehyde-sulphuric acid will give shades of reddish purple and violet with codein, heroin, ethylmorphin, peronin, papaverin, apomorphin, and apocodein and red-brown with thebain; Froehde's reagent will give blue with codein, green to blue with ethylmorphin, purple to blue with papaverin, crimson purple with heroin, blue to violet fading to brownish green and finally slate with peronin, and red-brown with thebain. The chloroform fraction in the main serves to substantiate the results obtained with the ether fraction and in the chloroform-alcohol fraction morphin will be indicated by its reactions with nitric acid, Froehde's reagent, and formaldehyde-sulphuric acid; narcein with sulphuric acid alone gives a deep-brown color

at the moment of solution, this changes to yellow, then green, and finally blue.

If one finds meconic acid, morphin and some of its associated alkaloids, he may feel reasonably certain that he is dealing with a product containing opium.

Kerbosch [1] describes a method of separating the opium alkaloids from each other. The mixed bases are extracted with a mixture of chloroform-alcohol 4–1 containing a trace of ammonia, the solvent evaporated and the residue dissolved in N/10 hydrochloric acid, narcotin is then partially precipitated by sodium acetate; sulphuric acid is added and papaverin thrown out by caesium cadmium iodide, the crystals being identified microscopically; narcein is then precipitated by sodium acetate and identified by the blue coloration imparted with iodin; thebain is also precipitated in presence of sodium acetate. The solution is then thoroughly shaken out with chloroform, ammonia added, the codein removed by benzol and morphin by chloroform-ether mixture, both being identified by the characteristic forms of their cæsium-cadmium-iodide compounds.

Plugge has also given a scheme for separating the opium alkaloids which deserves consideration. A solution of the free alkaloids is treated with sodium acetate which precipitates the narcotin and papaverin. The filtrate is set aside and the precipitate dissolved in the least quantity of hydrochloric acid and diluted with water to a $\frac{1}{4}$-per cent solution, from which the papaverin is precipitated by potassium ferricyanide, and after filtering and adding ammonia, the narcotin is shaken out with chloroform. The filtrate from the sodium acetate precipitation is concentrated and the narcein will crystallize out; it is filtered, concentrated sodium salicylate added and allowed to stand twenty-four hours for the thebain salicylate to crystallize. It is then filtered, acidulated with hydrochloric acid, and the excess of salicylic acid and any traces of thebain and narcein removed with chloroform. The solution is then concentrated, potassium sulphocyanide added, which precipitates the codein, it is filtered, ammonia added, any residual codein removed by ether, then acidified, heated to 60° C., ammonia added, and the morphin shaken out with chloroform-alcohol mixture.

When it is necessary to look for these alkaloids in lozenges or medicaments containing large quantities of gum, the sample should be dissolved in water, employing as small a quantity as possible, a little acid added and the solution poured into about ten times its volume of alcohol. This will precipitate the gum which soon coagulates and settles to the bottom or collects on the sides of the container. The solution contains the alkaloids and it may be filtered, neutralized and the alcohol evaporated, the rest of the separation being conducted as usual.

[1] Arch. Pharm., 248, 1910, 536.

Opium alkaloids may be detected without difficulty when they occur in mixtures containing at the same time the bases of ipecac, Hyoscyamus, and cinchona, though the reverse is not accomplished with the same facility for the brilliant color tests of the opium bases obscure the reactions of the other substances.

Atropin is readily identified when it occurs with morphin alone, for it is removed from alkaline solution by ether, leaving the morphin still in solution. The same condition prevails if strychnin, cocain, hydrastin, or Sanguinaria bases are present, they are all removed from an alkaline (caustic) solution by immiscible solvents, leaving the morphin. On subsequently adding ammonium chloride and shaking out with chloroform-alcohol mixture the morphin will be extracted. Acetanilid mixtures give up their acetanilid to chloroform in acid solution and caffein may be separated in like manner.

Codein may be identified when in mixtures with acetanilid or caffein by first shaking out these two substances from acid solution with chloroform. Colchicin may also be removed under the same conditions. Antipyrin cannot be satisfactorily separated from codein, but it may be identified when present, for it is partly removed from acid solution while codein is not, and codein gives certain reactions to which antipyrin does not respond. Apomorphin, heroin, ethylmorphin, and benzylmorphin will probably seldom if ever be found in admixtures with other bases.

Much attention has been given to the determination of morphin in opium products and many methods for accomplishing this purpose have appeared during the last ten years. Probably the greatest advance in evolving accurate, simple, and rapid methods has been attained at the Bureau of Chemistry of the U. S. Department of Agriculture and in 1909 Eaton [1] published his method for the estimation of morphin in opium, paregoric, laudanum, and cough mixtures. The writer has tried the method on many occasions and has found it most easy of application and accurate in its results, but like many other procedures in alkaloidal analysis it should not be attempted by a novice until he has familiarized himself with all its details. Following this work Buchbinder made an exhaustive study along the Eaton line of research and has communicated to me a modification of Eaton's method which bids fair to settle the many difficulties which have attended this important subject.

Eaton's method for the determination of morphin in opium was given in full on page 57. The adaptation of this procedure to opium preparations is given at this point.

[1] Bur. Chem. U. S. Dept. Agri. Bull. 137, p. 188.

ESTIMATION OF MORPHIN IN PAREGORIC

Evaporate 100 mils on the water-bath to a volume not exceeding 15 mils. Transfer to a separatory funnel, using no more than 2 or 3 mils of water at a time for the rinsings and no more than 15 mils in all. Shake out twice with 25 mils of ether, collect the ether and wash with 5 mils of water. Reject the ether and add the wash water to the main aqueous portion. To the latter add 30 mils of lime water, mix thoroughly, filter into a separatory funnel (No. 1), and wash with several small portions of lime water, using no more than 20 mils in all.

Proceed as in the method given for opium, beginning with the fourth sentence: "Shake out seven times with washed chloroform," etc.

ESTIMATION OF MORPHIN IN SYRUP PREPARATIONS

Take a convenient volume to yield between 30 and 75 milligrams of morphin. Make acid, then ammoniacal, and extract to complete exhaustion with a mixture of chloroform and alcohol, using large proportions of alcohol than that given above, if necessary to clear emulsions. In all cases do not consider the morphin exhausted until an actual test with 5 mils of the last shake-out, carried out as indicated above in the method for opium (Mayer's reagent), shows it to be free from alkaloid. Do not test before at least seven shake-outs (not including the last shake-out on a portion of which the test is to be carried out) have been made. Evaporate (on the water-bath) the combined chloroform-alcohol to dryness. Take up in 30 mils of lime water, filter into a separatory funnel, rinse, and wash several times with small portions of lime water, using about 20 mils in all.

Proceed as in the method for opium, beginning with the fourth sentence: "Shake out seven times with washed chloroform," etc.

Mr. Buchbinder's method for the determination of morphin as communicated to me is quoted herewith in full.

POWDERED OPIUM

Reagents:

Sodium hydroxide, 10 per cent.
Common salt.
Alkaline salt solution, made by saturating a 2 to $2\frac{1}{2}$ per cent sodium hydroxide solution with common salt and filtering.
Barium chloride, a saturated solution.
Concentrated hydrochloric acid.
Concentrated ammonia.
Alcohol.
Chloroform.
Methyl red (.2 per cent alcoholic solution), or Cochineal. (U. S. P.)

Digest 2 grams of powdered opium in 50 mils of water in a loosely stoppered Erlenmeyer for twenty minutes at a temperature between 90 to 100° C. While still hot add 20 mils of 10 per cent sodium hydroxide, and rotate gently. Allow to cool somewhat, stopper the Erlenmeyer and shake, not too violently, during ten minutes. Transfer the contents of the Erlenmeyer into a 200-mil graduated flask containing 18 to 20 grams of powdered common salt. Stopper and shake gently until the salt is dissolved. Rinse the Erlenmeyer and the stopper with several portions of alkaline salt solution, adding the rinsings to the graduated flask, and dilute with the same solution to a total volume of about 175 mils. Rotate so as to mix. Add 15 mils of a saturated solution of barium chloride. Reduce the froth by the addition of a little alcohol and make up to volume with alkaline salt solution. Stopper, shake thoroughly, then filter through a large, dry, fluted paper, if not clear, refilter.

By means of a pipette remove 100 mils of the filtrate, corresponding to half the weight of the sample taken and introduce into a separatory funnel No. 1. Add concentrated hydrochloric acid in portions—towards the end *not over* $\frac{1}{2}$ *mil at a time*—until acid to litmus; then add 4 mils in excess. Add concentrated ammonia in portions,—towards the end *not over* 4 *drops at a time*—until alkaline; then add 1 mil in excess. Add 10 mils of alcohol and shake out six times with chloroform, 30, 20, 20, 15, 15, and 15 mils respectively, filtering each successive shake-out through a piece of cotton wetted with chloroform and wedged in the neck of a small funnel, into a separatory funnel No. 2. Discard the liquid in separatory funnel No. 1.

To funnel No. 2 add 15 mils of alkaline salt solution, shake, then withdraw the chloroform layer into a separatory funnel No. 3. To funnel No. 3 add 5 mils of alkaline salt solution, shake, withdraw the chloroform layer into a beaker and add the alkaline salt layer to funnel No. 2. Return the chloroform to funnel No. 3, shake with a fresh portion of 5 mils alkaline salt solution, reject the chloroform layer and keep the alkaline salt layer for later use. Shake out the alkaline salt solution in funnel No. 2 twice with 25 mils of chloroform each time, collecting the chloroform in a separatory funnel No. 3. Shake funnel No. 3. Reject the chloroform layer and add the alkaline salt layer to the main alkaline salt solution in funnel No. 2.

To funnel No. 2 add concentrated hydrochloric acid *carefully*, reaching acidity within 2 *or* 3 *drops;* then add 1 mil in excess. Add concentrated ammonia *carefully*, reaching alkalinity within 1 *or* 2 *drops;* then add 5 drops in excess. Add 3 mils of water and 4 mils of alcohol. Shake out five times with chloroform, 30, 10, 10, 5, and 5 mils respectively, filtering each successive shake-out through cotton wetted with chloroform into a beaker.

Evaporate the chloroform on the water-bath to dryness. Add 10 to 20 mils of neutral alcohol and heat to dissolve. Add 3 drops of methyl red or 5 drops of cochineal. Add N/50 sulphuric acid until about 2 to 5 mils in excess. At this stage look out for any undissolved specks; heat again if necessary. If cochineal is used the alcohol should be almost entirely evaporated . If methyl red is used either evaporate the alcohol or else add water until a pure red tint is obtained. Titrate back with N/50 or N/100 sodium or potassium hydroxid which has been ascertained to be sufficiently free from carbonates to give a sharp end point with the indicator used.

One mil of N/50 acid corresponds to 6 mgms. of crystallized morphin. If more than 150 mgms. are indicated, repeat the analysis with a smaller quantity of the sample.

GUM OPIUM

Weigh out about 2 grams of gum opium in a beaker. Add 50 mils of water, cover with a watch glass and digest at a temperature between 90 to 100° until *thoroughly* disintegrated. Use a glass rod to mash particles. Transfer to an Erlenmeyer and while still hot add several portions of 10 per cent sodium hydroxide, using those same portions first to rinse the beaker, using in all about 20 mils. Allow to cool somewhat, stopper the Erlenmeyer and shake not too violently during ten minutes. Transfer the contents of the Erlenmeyer into a 200-mil graduated flask containing 18 to 20 grams of powdered common salt. Stopper and shake gently until the salt is dissolved. Rinse the Erlenmeyer and the stopper and also the beaker in which the digestion of the opium was made, with several portions of alkaline salt solution, adding the rinsings to the graduated flask, and dilute with the same solution to about 175 mils. Proceed as directed for opium, beginning with the seventh sentence in the first paragraph: "Rotate so as to mix."

LAUDANUM

Into a beaker to which has been added 40 mils of water and 20 mils of 10 per cent sodium hydroxide, introduce from a pipette or a burette 20 mils of laudanum. Stir with a glass rod, then transfer into a 200-mil graduated flask containing 18 to 20 grams of powdered common salt. Stopper and shake gently until the salt is dissolved. Rinse the beaker with several portions of alkaline salt solution, adding the rinsings to the graduated flask, and dilute with the same solution to a volume of about 175 mils. Proceed as directed for powdered opium, beginning with the seventh sentence in the first paragraph: "Rotate so as to mix."

PAREGORIC

Evaporate 200 mils of the sample to a volume of 50 or 60 mils. Transfer to a separatory funnel, rinsing the vessel in which the evaporation was made with several small portions of water, adding the rinsings to the separatory funnel. Shake out three times, 20 mils each time, with ether, collecting the ether in another separatory funnel. Wash the ether with 5 mils of water. Reject the ether and add the wash water to the main aqueous layer. Withdraw the latter into a beaker, rinse the funnel with several small portions of water, adding the rinsings to the beaker. Heat the beaker on the water-bath until all the ether is expelled. Add 20 mils of 10 per cent sodium hydroxid. Rotate so as to mix. Transfer into a 200-mil graduated flask containing 1 gram of powdered common salt for every 3 mils of the solution. Add 15 mils of water. Stopper the flask and shake gently until the salt is dissolved. Rinse the beaker with several portions of alkaline salt solution, adding the rinsings to the graduated flask, and dilute with the same solution to about 175 mils. Proceed as directed for powdered opium, beginning the seventh sentence in the first paragraph; " Rotate so as to mix."

THE DETERMINATION OF MORPHIN IN TABLET TRITURATES. DIRECT EXTRACTION METHOD, H. E. BUCHBINDER

Reagents:

Sodium chloride—finely powdered.
Ammonium chloride.
95 per cent alcohol.
Conc. ammonia—25 to 28 per cent.
Chloroform.
Neutral 95 per cent alcohol for dissolving the alkaloidal residue; 10 mils diluted with 20 mils of water to which has been added 3 drops of methyl red, should not require more then one drop of N/50 alkali to turn yellow.
Methyl Red—a 0.2 per cent alcoholic solution.
Standard N/50 sulphuric acid.
Standard N/50 or N/100 NaOH or KOH which is sufficiently free from carbonates to give a sharp end point with three drops of methyl red when used to titrate 5 mils of N/50 acid diluted with 20 mils of water.

Sample 600 mg.

Take a weighed amount of the powdered sample to yield not more than 140 mgms. of " crystallized " morphin. Brush into a 50-mil beaker. Fill a 50-mil measuring cylinder up to the 50 mark with water. Add 30 mils of the water in the cylinder to the beaker. Stir with a glass rod,

breaking up any lumpy particles, until the powder is dissolved as completely as possible (there may be left a small amount of insoluble material). Transfer to a separatory funnel containing 14 to 14½ grams of finely powdered sodium chloride and 1 gram (weigh within 100 mgms.) of ammonium chloride. Use the remaining 20 mils of water in the cylinder, in several small portions, to rinse the beaker, draining completely both the cylinder and the beaker. Stopper the funnel and shake till the salt has dissolved. Add 10 mils of 95 per cent alcohol. From a burette or a pipette add 0.5 mil of concentrated ammonia.

Immediately after the addition of the ammonia add 30 mils of chloroform containing 5 per cent alcohol, stopper, and shake *gently* for one minute. When the layers have separated and there is no emulsion, draw off the chloroform, filtering through a small filter paper wetted with chloroform, or through a small plug of cotton carefully wedged in the neck of a funnel and wetted with chloroform, into a beaker or flask. Repeat this process five more times with 15, 15, 10, 10, and 10 mils of chloroform respectively. In case of even slight emulsions the extraction of the alkaloid should be performed as follows. Draw off the chloroform layer together with the emulsified part into a second separatory funnel, and shake gently. In most cases the emulsion will dissappear or be greatly reduced. Draw off the chloroform, filtering into the beaker or flask. Treat the next shake-out in the same manner by drawing off both the chloroform and any emulsified part into the second separatory funnel, shaking and filtering. Repeat this process with each successive shake-out. In the case of emulsions not amenable to this treatment, the method as outlined cannot be used without suitable modifications.

Evaporate or distill off the chloroform on the water-bath. Dissolve the residue by warming with about 10 mils of neutral alcohol, add 3 drops of methyl red, run in standard N/50 sulphuric acid until the indicator has turned red, then add a few mils in excess. Heat on the water-bath to insure the complete solution of the alkaloid. After cooling, titrate back with N/50 or N/100 alkali.

One mil of N/50 acid corresponds to 6.00 mgms. of morphin $1H_2O$ (" crystallized "), and to 7.53 mgms. of morphin sulphate $5H_2O$.

DETERMINATION OF SMALL QUANTITIES OF MORPHIN

Small quantities of morphin present in opium in Chinese pills may be estimated very closely by converting it to heroin and weighing as such according to a procedure communicated to the author by Dr. H. A. Seil. The pills are exhausted with dilute acetic acid and if much gum is present the solution is poured into a considerable excess of alcohol and allowed to stand until the gum coagulates, after which it is filtered and the alcohol evaporated. The concentrated solution is transferred to a flask, 1–2 grams

anhydrous sodium acetate added, boiled with an excess of acetic anhydride, cooled, and transferred to a separator with water and in the presence of cracked ice. The acid solution is shaken two or three times with chloroform, separating the solvent and washing it with water, returning the latter to the acid mixture, and then the acid is neutralized with sodium bicarbonate, a slight excess being added. The heroin is then shaken out with ether and weighed after evaporating the solvent.

COLORIMETRIC ESTIMATION OF MORPHIN AND CODEIN

The estimation of small amounts of morphin or codein may be effected by the following colorimetric method of Carlinfanti,[1] a Wolff colorimeter being employed. The alkaloid is first isolated from the bulk of the sample by proper solvents, brought into solution with hydrochloric acid, and made up to a definite volume. In the case of morphin 1 to 5 mils are evaporated to dryness and cooled. The residue is dissolved in 5 mils of concentrated sulphuric acid, and the liquid introduced into a tube holding about 50 mils, fitted with a ground stopper; the dish is washed twice with 3 mils of concentrated acid, the washings added to the tube, which is then closed and immersed for fifteen minutes in a boiling water-bath. To the cooled tube is added 10 mils of a mixture of 100 mils of concentrated sulphuric acid and two drops of nitric acid (sp. gr. 1.4); on shaking, the characteristic blood-red color appears. The solution is then introduced into the cylinder of the colorimeter. An aliquot of a 0.5 per cent solution of morphin hydrochloride (1 mil or more) is evaporated and the residue treated in the same way. The solutions in the tube are then matched by the addition of small quantities of concentrated sulphuric acid.

In the case of codein the solutions of the sample and the standard are evaporated to about 1 mil by evaporation on a water-bath at 70-75°; 15 to 20 mils of monohydrated sulphuric acid are added cautiously so that the mixture is not heated. The liquid is then introduced into a 50-mil flask, the dish washed with 3 portions of monohydrated sulphuric acid, 5 mils each, and treated with 10 mils of a solution of monohydrated sulphuric acid 100 mils and 10 per cent ferric chloride 2 mils. After being shaken, the flasks are immersed for fifteen minutes in a water-bath at 80° C., the cooled solutions, which have assumed blue colorations, being introduced into cylinders of the colorimeter as before.

ESTIMATION OF CODEIN IN OPIUM

Dr. Caspari[2] has devised the following method for the estimation of codein in opium. Fifty grams of the sample are macerated with 500

[1] Boll. Chim. Farm., 1915, 54, 321. [2] Pharm. Review, 1904, 348.

mils of water for twelve hours with frequent agitation, filtered, and washed until the filtrate measures 750 mils, the residue is returned to the flask and shaken for fifteen minutes with 250 mils water, filtered and washed until this second filtrate measures 850 mils. The two filtrates are then combined, evaporated to 250 mils, treated with 5 grams barium acetate to precipitate the meconic acid and part of the resin, diluted to 700 mils, filtered, concentrated, and again precipitated with barium acetate. After filtering and washing the filtrate, a slight excess of 10 per cent sodium hydroxide is added which precipitates thebain, papaverin, and narcotin, leaving the codein, morphin, and narcein in solution; the mixture is filtered and washed after standing a short time. Concentrated hydrochloric acid is then added to neutralize the alkali, followed by an excess of 2 per cent ammonia water, and the flask allowed to stand for several hours and then filtered from the precipitated morphin, which is washed and the filtrate concentrated and the treatment repeated to remove additional morphin. The filtrate is rendered slightly acid with hydrochloric acid and concentrated to 75 mils, ammonia added in excess and the codein extracted with benzol. The solvent is then evaporated and the codein either weighed or titrated.

A. E. Andrews [1] claims that the morphin carries down some of the codein in the above method and recommends the following procedure. Twelve grams of dry opium are exhausted with successive small quantities of water and the filtered solution adjusted to 100 mils; 20 mils of 20 per cent lead-acetate solution added and after standing overnight, filtered rapidly on a Buchner filter; 100 mils of the filtrate, representing 10 grams opium, are subjected to a stream of hydrogen sulphide to remove the lead, filtered, the lead sulphide washed and the washings concentrated before adding to the main filtrate, from which the hydrogen sulphide is expelled by a current of air. The solution which should amount to no more than 130 mils is well shaken with 20 mils of a 20 per cent solution sodium salicylate and filtered from the resinous precipitate; a few crystals of thebain salicylate are added, the liquid stirred to facilitate the separation of any thebain as salicylate, and after standing overnight filtered through the same filter and the treatment repeated until no further separation occurs. The filter is then washed, the filtrate concentrated to 10–15 mils and while still warm, transferred to a separator, the rinsings being placed in a second separator. The solution is shaken three times with ether, the solvent each time being used for extracting the rinsings, and the aqueous solutions are then united and treated with 10 mils of 20 per cent sodium hydroxide and extracted four times with ether. The ether extracts are washed separately with two portions of water, united, dried with anhydrous sodium sulphate and distilled until only a few mils

[1] Analyst, 1911, 489.

are left when the codein crystallizes out. The alkaloid is dried *in vacuo* weighed and titrated.

CODEIN AND MORPHIN IN ADMIXTURE WITH CAFFEIN, ACETANILID, ACETPHENETIDIN AND QUININ

Dr. W. O. Emery [1] gives details of a method for the determination of codein, caffein, and acetphenetidin in pills and tablets of the cold and headache mixture type.

Weigh out about 0.3500 gram of powdered material (if in pill or tablet form at least ten of these should be reduced to powder), transfer to a separatory funnel by means of 10 mils very dilute sulphuric acid (or sufficient to render the solution decidedly acid after neutralization of any carbonate that may be present), extract by means of vigorous shaking with 50 mils of chloroform. After clearing, draw off the solvent, allowing it to run through a small (5.5 c.m.) filter into 200-mil Erlenmeyer. Distill off about 50 mils chloroform, using a small Bunsen flame. Extract a second and third time with the same amount of solvent as first used. Allow the chloroform from each extraction to run into the Erlenmeyer, then distill off all but about 10 mils. Now add 10 mils dilute sulphuric acid (1 volume concentrated acid to 5 of water) and heat on steam-bath until the chloroform has disappeared and only about 5 mils of the acid liquid remains, then treat as directed under caffein, page 837. Render the acid liquid in separator containing the codein sulphate neutral by the addition of solid sodium bicarbonate, wash out filter used in the preceding operation to clarify the chloroform, once with water, allowing latter to run into the separator, then re-extract three separate times with 50 mils chloroform. Collect solvent as above directed in a second 200-mil Erlenmeyer, distilling off most of the liquid by the aid of gentle heat. Transfer residual chloroform to a small beaker or evaporating dish, using sufficient fresh chloroform for this purpose, heat gently over steam-bath to dryness, cool, and weigh as anhydrous codein.

CAFFEIN, ACETANILID, QUININ SULPHATE AND MORPHIN SULPHATE IN MIXTURES. (W. O. EMERY.)[2]

Preparation of Sample and Solutions.—Transfer a separatory funnel an amount (containing not less than one-fourth grain of morphin) of the powdered sample equal to, or a multiple of, a unit dose, add 20 mils of water and 10 drops of dilute sulphuric acid, then extract with three 50-mil portions of alcohol-free chloroform, wash each portion in a second separatory funnel with 5 mils of water and add the combined washings to the alkaloidal solution in the first separatory funnel. Filter the chloroform

[1] U. S. Dept. Agri. Bu. Chem. Bull., 152, 239.

[2] J. Assn. Off. Agri. Chem., Vol. 1, page 360.

extracts through a small, dry filter into a 200-mil Erlenmeyer flask and distill by gentle heat to about 10 mils.

Caffein and Acetanilid.—The caffein and acetanilid will be present in the chloroform solution, while the quinin and morphin will be found in the acid liquid. If it is desired to separate and determine the caffein and acetanilid the analyst is referred to the methods described on pages 837.

Quinin Sulphate.—Add to the solution of quinin and morphin sulphates, 4–5 mils sodium hydroxide solution (1 to 10) and extract with four 40-mil portions of chloroform, wash each portion with 5 mils of water and pass the clear solvent through a small, dry filter into a 200-mil Erlenmeyer flask. Remove the solvent by gentle distillation and titrate the residual quinin with N/50 hydrochloric acid as follows:

Dissolve the amorphous alkaloid in 5 mils of neutral alcohol and titrate with N/50 hydrochloric acid to a faint red, using 2 drops of methyl red as an indicator. Heat on steam-bath until most of the alcohol has been expelled, adding, if necessary, sufficient acid to maintain the acid reaction. From the total number of mils of acid employed in the titration calculate the quinin sulphate.

1 mil N/50 HCl = 8.73 mg. quinin sulphate.

Morphin Sulphate.—Wash the filter, employed above, with 5 mils of water and add to the aqueous alkaline solution of the alkaloid. Now add 0.5 gram of ammonium chloride (or an amount slightly in excess of that required to free the morphin as well as convert all sodium hydroxide to sodium chloride) and, to the resulting ammoniacal solution, add 45 mils of chloroform and 5 mils of alcohol, then extract in the usual way, washing the solvent in a second separatory funnel with 5 mils of water. After clearing, pass the chloroform through a small, dry filter into a 200-mil Erlenmeyer flask. Repeat the extraction with three 40-mil portions of chloroform, washing and filtering as before, finally collecting all the solvent in an Erlenmeyer flask and distilling to about 10 mils. Transfer with chloroform to a small, tared beaker, evaporate to apparent dryness, add 0.5 mil each of water and neutral alcohol, start crystallization by stirring with a glass rod and finally evaporate to dryness. Cool and allow to stand until the weight becomes constant.

Check the weight of morphin, thus determined, by titration with N/50 sulphuric acid, using a drop of methyl red as an indicator. Dissolve the alkaloid in 1–2 mils of warm, neutral alcohol, then add the standard acid to a faint red. Evaporate most of the alcohol on a steam-bath, adding, if necessary, sufficient acid to maintain the acid reaction. From the volume of acid used calculate the morphin sulphate. One mil of N/50 sulphuric acid is equivalent to 7.58 mg. of morphin sulphate.

NOTE.—If the mixture contains acetphenetidin (phenacetin) in place of acetanilid, proceed as outlined above, except that the separation of caffein and acetphenetidin is conducted as directed on page 857.

SEPARATION OF HEROIN AND MORPHIN. (J. M. DORAN) [1]

The sample used should not contain over .2 gram of either heroin or morphin: if tablets dissolve in water slightly acidulated with hydrochloric acid; if solid, treat with water acidified with dilute hydrochloric acid and filter; if an alcoholic solution, make slightly acid with dilute hydrochloric acid and evaporate off the alcohol before proceeding.

Transfer the solution of the salts of the alkaloids to a separator, add a slight excess of ammonia, agitate with three separate additions of 25 mils each of carbon tetrachloride, passing each fraction of solvent through a 7-cm. dry filter into a tared dish. Evaporate on a steam-bath to dryness, heat at 100° for ten minutes, cool, and weigh as heroin. The weight may be checked by titration. Doran recommends N/25 acid and the results may be calculated to the salt by the following factors:

1 mil N/25 H_2SO_4 = 0.01622 gram heroin hydrochloride or diacetyl morphin hydrochloride.

1 mil N/25 H_2SO_4 = 0.1694 gram of the monohydrated salt, which is the commercial article, and account should be taken of this condition in reporting on sample where the question of the amount present is of moment.

For the determination of the morphin remaining as a free base in the ammoniacal solution the separations recommended above may be used to advantage.

SEPARATION OF CODEIN, HEROIN, AND MORPHIN. (DORAN)

If these three alkaloids occur in the same formula, the codein and heroin can be removed by carbon tetrachloride and weighed. The morphin can be determined in the ammoniacal solution as usual.

Another portion of the solution of the sample may then be treated with 10 mils of N/2 NaOH, which completely hydrolyzes the heroin to morphin with the use of heat. The codein may then be extracted from the alkaline solution by carbon tetrachloride and weighed, the alkaline liquor containing the other alkaloids is acidified, then made alkaline with ammonia and the total morphin determined.

GENERAL REMARKS ON THE ESTIMATION OF OPIUM ALKALOIDS

The separation of morphin from complex mixtures cannot be accomplished with the same ease as is the case with quinin, strychnin, cocain,

[1] J. Amer. Pharm. Assn., 1916, 163.

and others which dissolve readily in immiscible solvents. We have observed the comparative facility with which these alkaloids can be removed from mixtures in the crude condition, and their final separation and purification brought about with certainty. From most mixtures morphin can be separated and its determination accomplished with certainty, but the manipulations are not always simple.

Opium and ipecac alkaloids are very often combined in medicinal products, but the complete separation of the two groups is still a matter of research. Emetin can be separated from cephælin and of course morphin by shaking out with ether from a solution made alkaline with caustic alkali, but on subsequent extraction after rendering ammoniacal the cephælin will come out with morphin. It is probable that the ipecac alkaloids will be practically all removed by making the solution alkaline with ammonia and shaking out with ether and subsequently removing the morphin with chloroform-alcohol. The mydriatic alkaloids, strychnin, aconitin, cocain, quinin, hydrastin, and sanguinarin can all be separated from morphin by shaking out with ether and chloroform from a solution made slightly alkaline with caustic alkali.

When the sample consists of a pill or tablet of complex composition, the ground substance is extracted with alcohol, filtered, evaporated cautiously, the residue taken up with dilute acid and after adding alkali the alkaloids present are removed with ether or chloroform, and the morphin shaken out with chloroform and alcohol by either Eaton's or Buchbinder's procedure. Of course if the product contains opium, the other alkaloids will be contaminated with the opium bases other than morphin, and if it is a question of determining the other alkaloids also the problem under these conditions will become more or less involved.

Morphin pills can be dissolved in acidulated water, filtered from any insoluble material, and the morphin shaken out directly and purified. Tablets of morphin and atropin can be dissolved in acidulated water, the atropin shaken out with chloroform after rendering alkaline, and then after ammonia has been added the morphin can be removed by chloroform and alcohol.

Medicated lozenges should be dissolved in a small amount of water and the mixture, with any undissolved material, poured into an excess of alcohol about ten times the volume of the aqueous solution. After the gum has coagulated, the alcoholic solution is filtered off, the alcohol evaporated and the morphin separated from any accompanying alkaloids by the procedures mentioned above.

Opium suppositories or opium ointments should be treated with petroleum ether until the fats are all dissolved and the ether solution decanted through a filter, the residue washed with fresh petroleum ether and treated with acidulated water. The morphin can then be determined as in the

opium assay. Quinin sulphate has been found combined with opium in some pneumonia and croup remedies of the ointment class, and the quinin can be readily determined after the oils and fats are dissolved out with petroleum ether, by treating the residue with acidulated water, adding caustic alkali and shaking out with ether. On acidulating, adding ammonia and shaking out with chloroform-alcohol the morphin can be recovered.

Morphin can be determined in liquids of the chlorodyne type by evaporating a measured quantity of the sample until the solvent and volatile ingredients have been driven off, dissolving the residue in acidulated water, removing the coloring matter and acid constituents by shaking the acid solution with ether and then separating the morphin as usual.

Liquid preparations in general may be assayed for morphin according to Eaton's or Buchbinder's procedures with little preliminary manipulation, though if other drugs are of a resinous nature the solvent holding them in solution should be expelled and the residue then taken up with acidulated water and filtered from the resin.

Codein can be removed from alkaline solution without any difficulty with ether or chloroform, and it seldom occurs with other alkaloids except, of course, when it is present in opium. It is sometimes combined with antipyrin, and no satisfactory separation has been as yet evolved.

Heroin can be separated from its solutions by first shaking out the cold acid solution to remove neutral substances, and then freeing the heroin with sodium bicarbonate and extracting it with ether. The precautions to be observed in working with this substance have already been noted.

THE IPECAC ALKALOIDS

Emetin, $C_{25}H_{27}(OCH_3)_4$ (NH)N.

Cephælin, $C_{25}H_{27}(OCH_3)_3(OH)$(NH)N.

Psychotrin, $C_{25}H_{26}(OCH_3)_3(OH)N_2$.

The roots of several species of Ipecac contain the three alkaloids above mentioned.

Hesse [1] reports in addition to the above, hydroipecamin, isomeric with cephælin, and ipecamin, isomeric with psychotrin. He attributes slightly different formulas than those above which were determined by Carr and Pyman [2] and confirmed by Karrer.[3]

The United States Pharmacopœia recognizes two ipecacs, at least they are regarded by some authorities as distinct species, while in other quar-

[1] Annalen, 1914, 405. [2] Chem. Soc. Trans., 1914, 105, 1591.
[3] Ber., 1916, 49, 2057.

ters they are considered to be simply variations of the same species. They are designated Cephælis ipecacuanha, known commercially as Rio, Brazilian, or Para ipecac, and C. acuminata, known as Carthagena ipecac.

Rio ipecac is dark brown in color and closely annulated with thickened incomplete rings exhibiting transverse fissures with vertical sides; the bark is thick and light brown, easily separable from the yellowish white wood. Carthagena ipecac is usually thicker than Rio and is of a grayish-brown color, with fewer annulations which are occasionally transversely fissured with circular scars of bark; the bark is dark brown, smooth, and horny, the wood light brown. Both varieties have dark brown stems, wrinkled longitudinally.

It is generally reported that C. acuminata contains more cephælin in proportion to the emetin than is the case in C. ipecacuanha. Indian-grown root resembles Brazilian root more closely than Carthagena.

The official roots contain from 1.75 per cent to about 3 per cent of total alkaloids. There is also present a plant acid called ipecacuanhic acid, which is claimed to be a glucoside of the saponin class, and which is supposed to be the active constituent of the product known commercially as de-emetinized ipecac. This product is really a "de-alkaloided" ipecac, but it often contains considerable quantities of alkaloids. Finnemore and Braithwaite [1] have studied a substance which they claim is identical with ipecacuanhic acid and which they call ipecacuanhin. It appears to be a glucoside containing a catechol complex and yields on hydrolysis with emulsin a sugar producing an osazone, melting 207°. It is soluble in ether, petroleum ether, and hot water, but only sparingly soluble in chloroform. When given intravenously it had no physiological action on rabbits. Various plants have been offered for sale for ipecac, some being species of Cephælis, and others belonging to other genera. There are also a number of wild or false ipecacs, some of which have obtained more or less recognition in medicine:

Undulated ipecac from Richardsonia scabia.
Striated ipecac from Cephælis emetica.
American ipecac, Porteranthus gillenia stipulatus.
Indian Physic, P. trifoliatus; roots resemble P. gillenia but are not annulate.
Goanese ipecac, Naregamia alata.
East Indian Root, Cryptocorye spiralis.
White ipecac, Hybanthus ipecacuanha (Violaceæ).
White ipecac (Poaya blanca) Polygala angulata.
Anchieta salutaris.
Viola odorata.

[1] Pharm. J., 89, 136, 176.

Triosteum perfoliatum.
Heteropteris pauciflora.
The roots of several of the Euphorbiaceæ are used as emetics.
Ipecac spurge—Euphorbia ipecacuanha.
Purging or Emetic root—E. corallata syn. Tythymalopsis corallata.

Examination of samples of recent (1916–17) importations of ipecac has disclosed that Heteropteris pauciflora, Ipecacuanha fibrosa, and an Ionidium species have been substituted for true Cephælis.

Ipecac is noted for its emetic and expectorant properties, it is used in small quantities as a tonic and often occurs in remedies recommended for dysentery, dyspepsia, and pyorrhœa. Ipecac will be found in a number of combinations used in medicine, and the mixed alkaloids, under the name of " emetin," will be encountered occasionally as the sole active component of a pill or tablet. One of the best known products containing ipecac is Dover Powder, which consists of equal parts of powdered ipecac and powdered opium with sugar of milk. This mixture is sold as a powder, alone and in pills and tablets, and mercury mass; mercury with chalk, calomel, or quinin sulphate will sometimes be found as additional ingredients; combinations of ipecac and calomel; and ipecac and squill with ammonium salts are of common occurrence. Aloin, belladonna, strychnin, and ipecac is a mixture widely used, and some special laxatives include this combination with the addition of rhubarb, colocynth, and Podophyllum. Other mixtures include ipecac with strychnin, pepper, gentian, cloves, Capsicum, and sodium bicarbonate; with colocynth and mercury mass; with Conium; with morphin, potassium nitrate, and camphor; with mercury mass and Gelsemium; with Podophyllum and camphor; with acetphenetidin, quinin, aconite, and opium; with phosphorus, opium, and Digitalis sometimes with the addition of quinin; with strychnin, arsenous acid, reduced iron, quinin, or cinchonidin; with bismuth subnitrate and calomel; with nickel bromide, codein, lithium carbonate, and anise in anodynes for infants; with ammonium chloride, opium, licorice, and belladonna in cough mixtures; with opium, lead acetate, and camphor; with aconite, morphin, and tartar-emetic in fever compounds; with pepsin, Capsicum and Nux Vomica, gentian and sodium bicarbonate in antidyspeptic mixtures; with senega, tolu, cubeb, ammonium chloride, licorice, and Hyoscyamus in bronchial tablets; with Sanguinaria, morphin, atropin, aconite, tar, and tartar-emetic in cough mixtures; and with white-pine bark, wild cherry, squill, senega, Sanguinaria, opium, and potassium nitrate for the same purpose; with cerium oxalate for nausea. Lozenges of ipecac, and ipecac with morphin and antimony are well known.

Ipecac is combined with senega in a mixed fluid extract of the two drugs; with cimicifuga, senega, wild cherry, and licorice in a liquid com-

pound; and ipecac is dispensed in the form of wine and syrup both with and without opium. Syrup of morphin compound contains ipecac, senega, rhubarb, morphin, and oil of sassafras; and syrup of Irish moss (syrupus chondri compositus) contains Irish moss, ipecac, squill, senega, and opium.

Emetin

Emetin is an amorphous alkaloid, nearly colorless when pure, but becoming darker on exposure to light. It is strongly alkaline and completely neutralizes acids. It melts about 70° C., is optically inactive, is slightly soluble in water and petroleum ether, and dissolves readily in alcohol, ether, chloroform, and benzol.

It forms well-defined salts. The sulphate, acetate, and oxalate are amorphous and readily soluble in water. The hydrochloride is crystalline and also dissolves in water. The hydrobromide and hydriodide are sparingly soluble and separate on adding a soluble bromide or iodide to a solution of emetin hydrochloride. The nitrate is also sparingly soluble and may be obtained as a resinous mass on adding potassium nitrate to a solution of the hydrochloride.

When warmed on the water-bath with benzoic anhydride, emetin yields benzoyl emetin, which crystallizes from absolute alcohol in white needles, melting 185–186° C. The cooled melt should be dissolved in ether, the derivatives shaken out with dilute sulphuric acid, the acid solution treated with ammonia and shaken with ether. On evaporation, the benzoyl-emetin will be left and can be crystallized out of absolute alcohol.

Emetin hydrochloride boiled with ferric chloride, gives rubremetin hydrochloride, a scarlet substance, soluble in chloroform, melting, when air-dried, at 127–128° with decomposition.

Cephælin

This alkaloid, when freshly precipitated, is colorless but soon turns yellow. It is optically inactive. It melts at various temperatures, depending on the manner in which it is deposited. An alcoholic or ethereal solution on evaporation leaves the base as a transparent varnish. It may be obtained crystalline from an ethereal solution in a closed vessel. It is much more soluble in petroleum ether than emetin, and differs from that alkaloid by dissolving readily in alkali hydroxides.

Cephælin on methylation with sodium methyl sulphate and sodium amyloxide yields emetin, the OH group being methylated. With methyl sulphate and sodium methoxide the imino group is methylated principally, forming N-methyl cephælin, melting 194–195° C.

Psychotrin

Psychotrin occurs in small amount in ipecac. It crystallizes in yellow prisms, melting 138°, readily soluble in alcohol, chloroform, and alkalies, but only sparingly soluble in ether, thus differing from emetin and cephælin. Its solution in ammonia shows a blue fluorescence.

These alkaloids are always so intimately associated with each other that their analytical reactions will be discussed under one heading and not under the separate alkaloids.

The mixed alkaloids give an orange or lemon-yellow color when treated with a solution of calcium hypochlorite, followed by a drop of acetic acid.

They are precipitated from acid solution by the usual alkaloidal precipitants and yield various colors with sulphuric acid and oxidizing agents, but none of them are especially characteristic. Sulphuric acid produces a pale yellow becoming brown on warming.

Allen and Scott-Smith [1] have given details of a careful study of the color tests with special reference to the similarity of certain reactions with those given by the opium bases.

The authors have established that the alkaloids give with ferric chloride a blue color, later changing to green, while the opium alkaloids. produce a blue-green color from the very beginning.

Froehde's reagent gives with the ipecac alkaloids a purple-bluish-violet color, resembling the known reactions of the opium alkaloids but not such a pure color as afforded by morphin.

Iodic acid and starch frequently, but not always, give with the ipecac alkaloids the same blue color as with the opium alkaloids. Likewise both groups of alkaloids reduce in a similar manner the mixture of ferric chloride and potassium ferricyanide with the production of a blue color. The individual ipecac alkaloids exhibit different modifications and the reactions in part are not so sharp. Psychotrin appears to be the chief cause of the chief reaction with ferric chloride and iodic acid, but the possibility is not excluded that this reaction is produced by a new ipecac alkaloid, for if one treats the ipecac extract with lead acetate and decomposes the lead precipitate in the usual manner, a substance may be obtained with amyl alcohol from acid solutions, which at once reduces iodic acid, and mixture of ferric chloride and potassium ferricyanide. If the acid solution which has been extracted with amyl alcohol is made alkaline with sodium bicarbonate and again treated with amyl alcohol a residue is obtained which turns blue-green with ferric chloride, dirty purple red with Froehde's reagent, and blue with iron chloride and potassium ferricyanide. The ipecac alkaloids may to a certainty be distinguished from those of opium by the use of Froehde's reagent and hydrochloric acid.

[1] Pharm. Post, 1903, 348.

Emetin gives with Froehde's reagent a dirty-green color which turns grass-green on the addition of hydrochloric acid. Cephælin turns purple-red upon addition of hydrochloric acid and immediately changes to Prussian blue. Psychotrin gives with Froehde's reagent a dull-purple color which is turned dull-green by hydrochloric acid. The ipecac alkaloids collectively (total alkaloids) turn purple-bluish to violet with Froehde's reagent and after addition of hydrochloric acid (analogous to psychotrin) give an intense blue. Opium alkaloids with Froehde's reagent give a characteristic purple color which, however, is caused to disappear by hydrochloric acid.

Lowin [1] states that emetin and cephælin can be distinguished by the following tests: with Millon's reagent a 1–50 solution of emetin remains colorless in the cold, but turns yellowish on heating; a solution of cephælin turns violet in the cold and on heating becomes finally dark brown, while color changes are obtained very distinctly with a 1–1000 and are just visible with a 1–5000 solution. With mercuric acetate a 1–50 solution of emetin remains unchanged in the cold, and becomes somewhat yellowish and turbid on heating; a cephælin solution is colorless in the cold, but becomes violet and later dark grayish brown on heating, a 1–5000 solution of the alkaloid giving a distinctly visible reaction.

The microscopic examination of crystallized psychotrin furnishes valuable evidence in the detection of ipecac alkaloids. A chloroformic solution of the alkaloid is shaken with a little dilute acid, and the acid solution concentrated and transferred to a watch-glass or microscopic slide furnished with a cell. A watch-glass or beaker is then moistened on the inside with ammonia and inverted over the acid solution. The ammoniacal vapors are absorbed by the liquid and the alkaloid is liberated, separating in characteristic crystals. Psychotrin forms very minute crystals which appear to belong to the regular system, many of them appear to be octahedra and are very similar to microscopic crystals of arsenous oxide, while others closely resemble granules of rice starch.

In order to separate emetin and cephælin, a solution of the alkaloids in hydrochloric acid is treated with a slight excess of dilute potassium hydroxide and shaken with ether. The ether solution, after separating, is shaken with dilute alkali, and the latter, after washing with ether, is added to the original aqeous solution, which should now contain all of the cephælin, the emetin being in the ether, and may be obtained on evaporation. To recover the cephælin, the alkaline solution is treated with a slight excess of hydrochloric acid, then made ammoniacal and the alkaloid removed by a mixture of ether-chloroform (1–6).

A conclusive identification of these alkaloids when they are present in small quantities is not very satisfactory. It can often be stated with

[1] Chem. Zeit., 1903, 27, Rep. 25.

assurance that the residue under examination does not contain alkaloids giving sharply defined tests, though the reactions obtained may indicate emetin and cephælin. Again it is not always easy to detect these bases when other alkaloids are present. If ipecac alkaloids are suspected it is a good rule to use as much of the sample as can be spared so that a sufficient quantity can be obtained for preparing the identification tests.

The similarity between certain of the tests of these alkaloids and those of opium has already been noted, but any doubt as to the presence of the latter may be set at rest by treating a portion of the residue with formaldehyde-sulphuric acid, which gives the characteristic purple with opium bases.

The tests given by the Nux Vomica and belladonna alkaloids are not obscured by the presence of the ipecac bases.

In case it becomes necessary to determine the presence of ipecac bases in a complex mixture of alkaloids, the best plan is to separate the cephælin by taking advantage of its solubility in alkali hydroxides by a procedure similar to that described above for separating emetin and cephælin. After recovering the latter and establishing its identity, the presence of ipecac in the sample may be asserted.

ALKALOIDS FROM HYDRASTIS CANADENSIS, BERBERIS AQUIFOLIUM AND OTHER SPECIES OF BERBERIS, AND ALLIED ALKALOIDS

Hydrastin, $C_{21}H_{21}NO_6$.
Hydrastinin, $C_{11}H_{13}NO_3$.
Berberin, $C_{20}H_{17}NO_4$.
Canadin, $C_{20}H_{21}NO_4$
(*l*-tetrahydroberberin).
Nandinin, $C_{19}H_{19}NO_4$.
Oxyacanthin, $C_{19}H_{21}NO_3$ or $C_{18}H_{19}NO_3$.
Berbamin, $C_{18}H_{19}NO_3$.
Jeteorrhizin, $C_{20}H_{19}NO_5$.
Columbamin, $C_{21}H_{21}NO_5$.
Palmatin, $C_{21}H_{21}NO_6$.

The most important alkaloid of this group is hydrastin, which occurs in the rhizome of Hydrastis canadensis (Ranunculaceæ), Golden Seal, in amounts varying from .5 to 3 per cent, and is accompanied by canadin and berberin. Berberin is widely distributed, being found in Hydrastis, the roots of Berberis aquifolium (Berberidaceæ) or Oregon grape, B. vulgaris, common barberry, B. nervosa, B. pinnata and others, Coptis trifolia (Ranunculaceæ), gold thread, C. teeta, and probably many other botanical species. Oxyacanthin accompanies berberin in the Berberis

genus, and berbamin is found in B. vulgaris. The last three alkaloids mentioned have been isolated from the root of Jeteorrhiza Calumba, Calumba root which was formerly supposed to contain berberin, and they were probably mistaken for this alkaloid.

Hydrastis, owing to its high intrinsic value, is liable to adulteration, and samples of the ground drug should always be examined very carefully under the microscope. It will be found mixed with some of the native root drugs, serpentaria, Cypripedium, senega, Collinsonia, Jeffersonia, Trillium, etc., and according to Lloyd the whole drug has been found wholly or in part substituted by Stylophorum diphyllum.

Preparations containing Hydrastis, or the alkaloids hydrastin and berberin, are used for a number of different purposes. Golden Seal has tonic properties, and is claimed to increase the intestinal secretions and promote the flow of bile. It is used in gastric catarrh, dyspepsia, and for troubles affecting the mucous membranes of the mouth, throat, nose, and genito-urinary organs, and the alkaloids should be sought in medicines exploited for these purposes. Berberis is used as a tonic and blood purifier, in syphilis, scrofulous complaints, psoriasis, etc., and Coptis trifolia has long been known as a remedy for canker and various forms of ulcerated and sore mouth. The latter is often administered as a masticatory, and is combined with other drugs in gargles and bitter tonics.

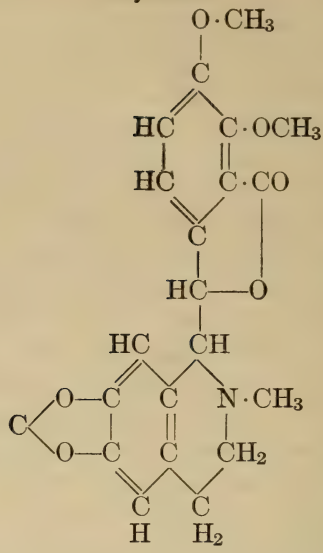
Of the combinations met with in practice may be mentioned pills and tablets containing the extract of Hydrastis with morphin and certain astringent substances as alum, zinc sulphate, tannic acid, guaiac, boric acid, etc., sold for astringent washes and uterine antiseptics; berberin and podophillin, and extract of Berberis aquifolium and Cascara sagrada; elixirs containing Berberis with Cascara and licorice; berberin and iron pyrophosphates; Hydrastis, rhubarb, and potassium bicarbonate; tonics containing Hydrastis, senna, iron, and aromatics; utero-ovarian sedatives and anodynes containing Hydrastis, Viburnum prunifolium, and Piscidia piscipula (Jamaica Dogwood), this same mixture being sold also in tablet form.

Hydrastin is sold in the form of tablet triturates, and the hydrochlorate has considerable use in eye remedies. Hydrastinin hydrochlorate, prepared synthetically from hydrastin, is used in menorrhagia and for arresting postpartum hemorrhage.

The term "Hydrastin" is also applied to a concentrated resinous extract obtained from the root.

Calumba root is a mild, non-astringent tonic, and as it contains no tannin may be combined with iron, hence it may be suspected in iron tonics. In tablet form it is offered combined with Nux Vomica, Cinchona, gentian, phosphorus, and chamomile. In liquid form it is used with ginger, senna, and other tonics, aromatics, and mild cathartics.

Hydrastin



Hydrastin, the white alkaloid of the Golden seal root, occurs in nature partly in the free state and partly combined. It crystallizes from alcohol in prisms, melting at 132° C., insoluble in petroleum ether, very slightly soluble in water, but dissolving in chloroform, benzol, ether, and alcohol, chloroform being by far the best solvent. It is a weak base, insoluble in alkalies, and may be completely removed by chloroform from solutions acidified with hydrochloric acid, resembling narcotin in this respect, to which it is closely related constitutionally. Its solutions in solvents are strongly dextrorotatory, and its acid solution is lævorotatory. It is precipitated by most of the ordinary alkaloidal precipitants, potassium bichromate and picric acid, but does not give precipitates with bromine water nor potassium iodide as is the case with berberin. The picrate, recrystallized from boiling alcohol, forms lustrous yellow needles, melting 165–170° C.

The precipitate formed with bichromate becomes bright red or pinkish violet when touched with concentrated sulphuric acid, differing in this respect from the colors given by strychnin or gelsemin under similar conditions.

Hydrastin yields protocatechuic and formic acids when fused with potassium hydroxide. On treatment with oxidizing agents opianic acid and hydrastinin are formed, according to the equation:

$$C_{21}H_{21}NO_6 + H_2O = C_{10}H_{10}O_5 + C_{11}H_{13}NO_3$$

Sulphuric acid when pure gives no color with hydrastin, but in the presence of potassium bichromate a brown color, changing to pinkish

violet, is produced; neither manganese dioxide nor hydrogen dioxide give any color. A solution of hydrastin in dilute sulphuric acid gives a yellow precipitate with bichromate, the precipitate when freed from liquid and touched with sulphuric acid gives a pink-violet color, soon fading.

Ammonium vanadate reagent produces a pink coloration, soon changing to bright red and then gradually to brick red, entirely different from that produced with strychnin. Froehde's reagent, freshly prepared, gives no reaction when first added, but on standing a deep-green color gradually develops. Sulphuric acid containing formaldehyde causes no color, in marked contrast to narcotin, which gives a purple. With nitric acid a yellow shade is produced, but there is nothing characteristic about it.

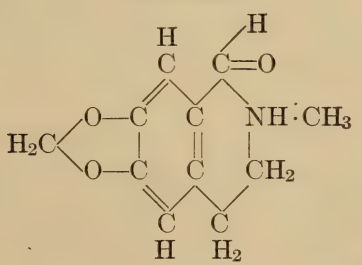
A solution of hydrastin in dilute sulphuric acid develops an intense blue fluorescence when a drop or two of N/10 permanganate is added. The fluorescent substance is not removed by ether or chloroform, differing thereby from esculin.

Labat [1] makes use of the formation of opianic acid for detecting hydrastin. The alkaloid is oxidized in acid solution with permanganate and then alcohol added, the concentration being adjusted in order to obtain a 1 per cent solution of opianic acid. 2-mil portions of concentrated sulphuric acid are treated with 0.1 mil of the alcoholic solution and then tested with certain phenols; 0.1 mil gallic acid produces a blue color, fading to brown on warming; guaiacol, red changing to blue; α-naphthol, a gooseberry red; β-naphthol, a wine red; codein, violet to blue; β-methylnaphthol, violet soon fading. The same reactions are observed with narcotin and hydrastin.

Hydrastin forms condensation products with acetone and certain other ketones.

The salts of hydrastin which occur on the market are the hydrochloride and sulphate. The hydrochloride is readily formed when a solution of the alkaloid in absolute ether is brought in contact with hydrogen chloride gas. Both salts dissolve readily in water. The hydrobromide and hydriodide also occur, but have little or no use in medicine. The hydriodide is the least soluble of the four.

Hydrastinin



[1] Bull. Soc. Chim., 1909, 5, 743.

Hydrastinin in the form of its hydrochloride has a limited use in medicine and is an artificial alkaloid, produced, together with opianic acid, on oxidizing hydrastin. The crystalline hydrochloride is formed by passing dry hydrogen chloride through a chloroform solution of the base.

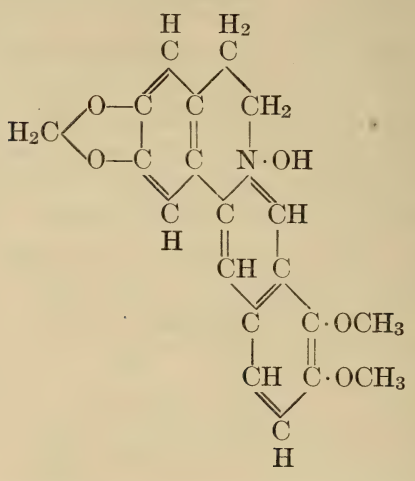
Hydrastinin crystallizes in needles, melting 116–117°, slightly soluble in water and dissolving readily in the ordinary organic solvents, including petroleum ether. It is inactive. Its solution in water is alkaline and exhibits fluorescence and its alcoholic solution is fluorescent. It combines with hydroxylamine and forms benzoyl and acetyl derivatives.

A solution of the hydrochloride when treated with a few drops of Nessler's reagent gives a precipitate which blackens instantly. Morphin, apomorphin, and picrotoxin also reduce Nessler's reagent and are, according to Jorissen, the only other principles which give a reaction similar to hydrastinin. It also reduces Tollen's reagent.

The color reactions given by hydrastinin with concentrated sulphuric acid, ammonium vanadate, and Froehde's reagent are the same as those given by hydrastin. Its solution in dilute sulphuric acid, when treated with a drop or two of permanganate, shows fluorescence on dilution.

Hydrastin on benzoylation with benzoic anhydride or benzoyl chloride yields a benzoylated compound melting 98–99° when crystallized from dilute alcohol. When warmed with acetic anhydride in benzole solution it yields an acetyl derivative, melting 105°.

Berberin



When pure, berberin is a yellow alkaloid, the melting-point of which has not been definitely determined. It usually contains varying amounts of water which, according to some authorities, is entirely driven off at 100° C. Most of its salts are less soluble in water than the free alkaloid,

thus the hydrochloride requires 500 parts of water to keep it in solution, and is nearly insoluble in dilute hydrochloric acid.

It has a bitter taste, is a weak base somewhat soluble in cold water, alcohol, and amyl alcohol, and readily soluble on warming, slightly soluble in chloroform and benzole, and insoluble in ether and petroleum ether. Chloroform and benzole will remove it from both acid and alkaline solutions to a limited extent, but it is best removed from solutions by a mixture of alcohol and choloroform. It is readily separated from oxyacanthin and hydrastin through its insolubility in ether.

Berberin forms crystalline derivatives with acetone and chloroform, from which the free base may be liberated by warming in alcoholic solution.

Berberin is precipitated by nearly all of the ordinary alkaloidal precipitants, Mayer's and Wagner's reagents, potassium iodide and chromate, picric acid, platinic chloride, gold chloride, bromin water, and hydrochloric and sulphuric acids if not too dilute. Concentrated sulphuric acid dissolves berberin to an orange-yellow solution, which becomes olive green on warming, and on adding bichromate a violet shade changing to brownish green takes place. Under some conditions, depending on the purity of the residue, a black color will be observed on adding the oxidizing agent, soon changing to chocolate brown and then violet.

Froehde's reagent produces a greenish brown to dark brown or violet. Nitric acid dissolves berberin to a dark reddish-brown liquid, which on dilution with water gives a yellow precipitate partially soluble in ammonia. When a solution of berberin strongly acidified with hydrochloric or sulphuric acids is treated with a small quantity of chlorine water, cautiously added from a pipette and allowed to rest on the surface of the liquid to be tested, a zone of bright red is formed at the junction of the two liquids. A fragment of sodium nitrate stirred into a solution of berberin in concentrated sulphuric acid gives a violet streak.

Canadin, *l*-tetrahydroberberin

This alkaloid, in the lævo form, is present in small amount in Hydrastis root; it melts 132.5–137° and is soluble in the ordinary organic solvents with the exception of petroleum ether, which dissolves it sparingly. It is insoluble in water. An alcoholic solution of iodine converts it into berberin.

Tetrahydroberberin occurs in three forms, the dextro modification melting at 139–140°. The racemic form splits into its constituents by precipitating with ortho-bromcamphorsulphuric acid. Hlasewitz and Gilm obtained tetrahydroberberin, melting 167°, by reducing berberin with zinc and sulphuric acid.

Canadin liberates iodine from iodic acid and gives Prussian blue with potassium ferricyanide and ferric chloride. Its color reactions are not especially characteristic; sulphuric acid dissolves it to a yellow solution, gradually turning red, and nitric acid gives a yellow solution. Ammonium vanadate gives an olive-green color turning to dark black-brown.

Oxyacanthin

Oxyacanthin accompanies berberin in several species of Berberis and is readily separated from berberin by its solubility in ether. When thrown out of an acid solution with ammonia it is obtained in an amorphous form melting 138–150°. It may be crystallized out of alcohol or ether in the form of needles melting at about 210°. It is dextrorotatory and soluble in organic solvents, sparingly in petroleum ether, and partly removed from its acid solution by chloroform. The form in which it ordinarily occurs is known as the alpha modification, and as such, is soluble in sodium hydroxide with great difficulty; on treatment with potassium or barium hydroxide it is converted into the beta form which is readily soluble in potassium hydroxide, and cannot be removed from such a solution with ether. Ammonium chloride precipitates the beta modification from its solution in potassium hydroxide and this precipitate on drying goes over to the alpha form.

Oxyacanthin liberates iodine from iodic acid, from potassium iodide in dilute sulphuric acid, and gives Prussian blue with ferric chloride and potassium ferricyanide. With Froehde's reagent it gives a violet color turning blue or green and gradually fading to yellow. Ammonium vanadate gives a dirty violet.

Berbamin

This alkaloid occurs with oxyacanthin and berberin in Berberis and may be separated from the former by petroleum ether in which it is insoluble. The free base melts 197–210° according to Rudel. Its color and reducing reactions are similar to those of oxyacanthin.

Nandinin

Eykman reported this base as occurring in the root of Nandina domestica, but its properties and composition have apparently never been published.

When these alkaloids of Calumba are extracted from liquid mixtures the residue is easily mistaken for berberin, the color reactions are somewhat similar and the precipitates obtained and general character of the mixture suggest this alkaloid. For this reason the absence of calumba bitter, " calumbin " should be established unless one is certain that he

is dealing with a berberin-bearing drug instead of calumba. The three alkaloids from calumba all form yellow salts.

Columbin

This substance is a neutral principle and is intensely bitter. Investigation has demonstrated that it is a chemical individual, probably of lactone constitution, possessing two hydroxyl groups and melting at 182° C. Its formula is given as $C_{28}H_{30}O_9$. It gives a diacetyl derivative, melting at 218° and crystallizing in white needles. Pure columbin is slightly soluble in cold water, alcohol, and ether, but goes into solution more readily on warming. It may be removed from an acid aqueous solution by shaking out with ether, and the residue left on evaporation purified by crystallizing the columbin out of alcohol or ether, decolorizing if necessary by shaking with dry animal charcoal and filtering.

Columbin gives an orange color changing to red on treatment with concentrated sulphuric acid, the solution throwing out brown flocks on dilution with water. Boiling alkalies and lime water convert columbin to columbic acid, melting 228°, slightly soluble in ether and water and readily soluble in alcohol.

Columbin is not precipitated by the usual organic precipitants, and may be removed from an acid solution by ether after precipitating the alkaloids by Mayer's reagent.

In this group the analyst will be concerned chiefly with the separation and identification of berberin, hydrastin, and hydrastinin, and occasionally to identify columbin, and to differentiate between the columba alkaloids and those from Berberis. The other alkaloids mentioned are not used commercially. Berberin or hydrastin, when alone, are easy of identification. Mixtures containing Hydrastis nearly always give indications of the presence of this drug through the fluorescence imparted to the ether shake-outs.

In order to remove the alkaloids from the rest of the drug, and the other ingredients in the medicine, the sample or an evaporated residue of a liquid portion should be triturated four or five times with successive portions of 95 per cent alcohol in an evaporating dish, the united alcoholic extractions evaporated over the steam-bath, and the residue dissolved in dilute acid and subjected to the regular scheme of alkaloidal separation.

Hydrastin may be completely separated from berberin by shaking out with absolute ether from a slightly alkaline solution, and berberin may be subsequently removed by alcohol-chloroform mixture. As obtained in this way, hydrastin will be contaminated with canadin, which may be separated from hydrastin by dissolving the residue in dilute acid, rendering alkaline and shaking out with petroleum ether, in which hydrastin is almost insoluble. If the drug product under investigation contains

Berberis, the ether will remove oxyacanthin and berbamin. Berberin may also be removed from a residue of mixed alkaloids by dissolving in alcohol, diluting with water and precipitating with 10 per cent potassium iodide.

It will often happen that some of the oxymethylanthroquinone drugs will be present in mixtures with Hydrastis or Berberis, and the residues obtained therefrom will be contaminated with substances which will alter the color tests. These bodies may be eliminated by shaking the ethereal solutions of the alkaloids with dilute ammonia; or the alkaloids may be precipitated from an acid solution by Mayer's reagent, the precipitate filtered, washed, dissolved in alcohol, and the alkaloids again liberated by alkali and removed by suitable solvents after diluting the solution with water.

Quantitative Estimations.—For the estimation of hydrastin in pills or tablets containing Hydrastis extract, the sample should be ground and triturated in a mortar with 95 per cent alcohol, the alcoholic extract filtered into an evaporating dish, the procedure repeated three times, and the filter finally washed with a fresh portion of alcohol. About 10 mils of water are then added to the contents of the dish and the alcohol evaporated over the steam-bath. The residue is then treated with water and dilute sulphuric acid, filtered into a separator; ammonia added in slight excess and the hydrastin removed by shaking out four times with absolute ether. The ethereal extract is shaken out with dilute hydrochloric acid, the acid solution rendered alkaline with ammonia, and the hydrastin removed by shaking out four times with ether. The ether extract is then washed once with water, filtered into a tared dish, the solvent evaporated and the residue weighed as hydrastin.

If the sample is a liquid it should be evaporated over the steam-bath until the alcohol and water are expelled, the residue treated with alcohol and the determination finished as above.

Berberin may be determined, when it occurs in mixtures with hydrastin, by precipitating the acid solution with potassium iodide which removes the berberin. The hydrastin may then be determined in the filtrate and the berberin converted into the acetone compound and the estimation completed according to Gordin's [1] method. The procedure is as follows: the precipitated hydriodide is washed with a 2 per cent solution of potassium iodide and then washed into a flask; after heating to 60–70°, acetone is added to the extent of one-third the volume of the water, and the mixture shaken for ten minutes; 5 mils of sodium hydroxide 10 per cent are added and the liquid shaken until the hydriodide has disappeared; the mixture is then diluted with three times its volume of water and allowed to stand overnight. The berberin-acetone is filtered off onto a Gooch crucible, dried first in a vacuum and then at 105° and weighed, 1 gram

[1] Arch. Pharm., 1901, 239, 638.

of the compound corresponds to 0.853 gram of berberin. To correct for the berberin-acetone compound dissolved in the mother liquor 0.0000273 gram is added per mil.

In the event of the products containing berberin alone, or with oxyacanthin and berbamin, the preliminary treatment of the sample will follow the procedure described above and the oxyacanthin and berbamin removed by shaking out with ether after rendering alkaline; the solution is then acidulated, the berberin precipitated with potassium iodide and the determination completed by forming the acetone compound.

Berberin may be determined titrimetrically by precipitating the hydrochlorate with potassium-naphthalin thiosulphonate, and titrating the excess of thiosulphonate with N/100 iodine.[1] The thiosulphonate is added in excess to the solution of the alkaloid, the precipitate is filtered off, and the filtrate and washings titrated with the iodine. Each mil of the N/100 thiosulphonate solution corresponds to .003351 gram of berberin.

Hydrastin is readily separated from morphin on account of its solubility in ether. In mixtures containing both alkaloids, after the preliminary treatment, a slight excess of fixed alkali is added and the hydrastin removed by shaking out with ether; a little ammonium chloride is added and the morphin shaken out with chloroform-alcohol 2–1.

ALKALOIDS OF THE CORYDALIS GROUP

The Corydalis genus, Papaveraceæ, embraces about 100 species, several of which have been employed in medicine. In our Materia Medica the term relates to the Turkey or Squirrel-corn, Bicuculla canadensis syn. Corydalis canadensis. The plant is small, resembling the common Dutchman's Breeches (B. cucullaria) a closely related species, and has a yellow blossom and finely slashed leaves. It grows in moist, rich woods. The tubers, which constitute the drug, are small, roundish, with a slight peculiar smell, and a bitterish somewhat pungent and persistent taste.

The drug is a tonic, diuretic, and slightly alterative, and in these particulars resembles gentian, calumba, and other simple bitters. It has been employed in syphlitic, scrofulous, and cutaneous troubles, generally in the form of a liquid extract and with other drugs. It will be found in elixirs and syrups containing potassium iodide, Stillingia sylvatica, Xanthoxylum americanum, and Iris versicolor; or with Stillingia, Iris, Chimaphila umbellata (Pipsissewa or Prince's pine), Sambucus canadensis, Xanthoxylum berries, and coriander.

The alkaloids of B. canadensis have not been carefully studied and hence we are uncertain whether or not they are the same as occur in Corydalis cava. Kraemer reports that they resemble the alkaloids of B. cucullaria, and that corydalin is one of them.

[1] Arch. Pharm., 1900, 238, 6.

C. cava has been the source of practically all the material used in researches on these bases. The bulk of the work has been done by Gadamer, Ziegenbein, Dobbie and Lauder, and Makoshe and it will be given a brief summary here.

Gadamer divides the alkaloids into three large groups and one of these is subdivided.

I. Weak bases giving yellow berberin-like derivatives with alcoholic iodine

Corydalin, $C_{22}H_{27}NO_4$ ..... *m.* 134–5°
Corybulbin ..... *m.* 238–9°
Isocorybulbin $C_{21}H_{25}NO_3$ ..... *m.* 179–80°

II. Medium bases, not acted upon by alcoholic iodine.
Corycavin, $C_{23}H_{23}NO_6$ ..... *m.* 216–17°
Corycavamin, $C_{21}H_{21}NO_5$ ..... *m.* 149°

III. Strong bases.
1. Bulbocapnin, $C_{17}H_{13}N(OCH_3)(O_2CH_2)OH$ ..... *m.* 199°
Corydin, $C_{17}H_{13}N(OCH_3)_3(OH)_2$ ..... *m.* 103–5°
Corytuberin, $C_{17}H_{13}N(OCH_3)_3OH$ ..... *m.* 240°
2. Dicentrin.
Glaucin.

All of the above bases are removed from alkaline solution with ether except corytuberin, which is subsequently removed by chloroform.

It is somewhat conflicting to place glaucin in a group of strong bases when it has been described among the Sanguinaria and Chelidonium alkaloids as a weak base, which can be removed from acid solution by chloroform, but the author assumes no responsibility for Gadamer's grouping.

Gadamer also reports protopin in the leaves of C. cava, and Heyl [1] reports its presence in the tubers of C. solida.

Corydalin crystallizes from alcohol in prisms insoluble in alkalies, but somewhat soluble in water, and readily in organic solvents. When treated with iodine in alcoholic solution it is oxidized to dehydrocorydalin which closely resembles berberin. On reducing this substance, two isomeric inactive corydalins are formed, one melting 158–9° and the other 135°.

To identify corydalin, Mulliken recommends the preparation of the nitrate, which melts with considerable ebullition from 193–200° C. The alkaloid is treated with dilute nitric acid (1–20) and well macerated. The liquid is carefully decanted, the residue dried on a porous tile, dissolved in a small quantity of boiling water, filtered hot, and the nitrate allowed to crystallize by spontaneous evaporation.

[1] Apoth. Zeit., 1910, 25, 36.

Corybulbin may be separated from corydalin by dissolving the bases in hydrochloric acid, adding excess of sodium hydroxide which precipitates corydalin only, and after removing the latter, corybulbin is precipitated by carbon dioxide; or it may be separated by treating crude corydalin with hot alcohol until most of the corydalin is dissolved, and then boiling with a large quantity of alcohol, from which the corybulbin separates as a fine crystalline powder. It is nearly insoluble in water and ether, soluble with difficulty in alcohol and readily in chloroform. It can be converted into corydalin by treatment with equivalent quantities of methyl iodide and potassium hydroxide in methyl alcohol. It reacts with iodine to produce lemon yellow needles.

The color reactions of some of the bases of this group are reported as follows:

Reagent	Corydalin	Dehydro-corydalin	Bulbocapnin	Corycavin	Corybulbin
Sulphuric acid	After some time red and violet		Orange gradually violet-red violet.	Dirty green-brown violet	
Nitric acid	Yellow	Yellow	Reddish to brown	Red	Yellow
Erdmann's reagent	Yellow-green-violet	Yellow-green-violet	Blue-bluish violet	Dirty green	Yellow
Froehde's reagent	Yellow-pale green-blue	Yellow-blue	Dark blue	Dark Green	Red-brown green
Sulpho-vanadic acid	Yellow-green-blue	Yellow-green-blue	Bright olive-blue	Dark green	Brown-green

The possibility of confusing an alkaloidal residue from Corydalis with one from Chelidonium must be emphasized.

GELSEMIUM AND ITS ALKALOIDS

Gelsemin, $C_{20}H_{22}N_2O_2$.

Gelseminin.

Semperviren.

The rhizome of yellow jasmine or jessamine, Gelsemium sempervirens (Loganiaceæ), official in the Pharmacopœia, contains the first two alkaloids above mentioned, and possibly the third.

In addition to the basic constitutents, the drug contains about 4 per

cent of resin, emodin monomethyl ether, ipuranol, scopoletin, the monomethyl ether of æsculetin, both free and in the form of a glucoside, and some sugar.

Gelsemium is antipyretic and antizymotic and induces paralysis of sensibility and motility. It is used in neuralgic conditions, for ague, malaria, and sometimes for treating the morphin and liquor habits. Morphin, alcohol, and to some extent atropin are physiologically antagonistic.

The drug is offered in the form of its fluid, solid and powdered extracts, as a concentration "gelsemperin"; and the alkaloid gelsemin is employed in the form of the hydrochloride.

Gelsemium is combined with the Cinchona alkaloids and Capsicum in ague pills; with arsenic and ferrous sulphate and sometimes with strychnin and Podophyllum in malaria and periodic pills; with mercury and ipecac for desentery. In tablet form it occurs combined with acetanilid, caffein, and sodium bicarbonate; with acetanilid, camphor monobromate, sodium salicylate, and Hyoscyamus for migraine. It is combined with codein, acetanilid, caffein and bromides in elixirs, and also with coca. Gelsemin hydrochloride is sometimes administered in the form of hypodermic tablets. Some confusion exists as to the nomenclature of the Gelsemium bases and Merck's description of gelseminin really applies to gelsemin as it is known to English writers.

Gelsemin

This alkaloid crystallizes in white glistening prisms, melting 178°, readily soluble in ether, chloroform, and alcohol, and sparingly soluble in water. Its solutions are dextrorotatory. Its constitution has not been determined and it is only within recent years that Moore obtained a product sufficiently pure to establish its composition as $C_{20}H_{22}N_2O_2$. It is a strong base and is precipitated by the usual alkaloidal reagents.

Mulliken gives the composition of this alkaloid as $C_{22}H_{26}O_3N_2$, with a melting-point of 160° when dried in a desiccator, and 172° when dried at the temperature of boiling xylol or toluol.

When pure it dissolves in concentrated sulphuric acid without color; and on the addition of an oxidizing agent, an intense red or purplish-red color develops, passing gradually to blue or bluish green and finally to blue or green. As gelsemin is nearly always contaminated with more or less gelseminin, the color obtained with sulphuric acid alone is reddish or brown gradually changing to pink, and on heating purple and chocolate colored tints appear. The colors obtained on adding oxidizing agents to a sulphuric acid solution of an impure gelsemin are red to purple, with purplish-red streaks following the course of the oxidizing agent, finally becoming blue-green. If cereso-ceric oxide is used, the red coloration is very intense.

A solution of gelsemin in concentrated nitric acid reddens on warming and finally becomes dark green. The pure alkaloid dissolves in nitric acid with little or no color, and on allowing the liquid to evaporate spontaneously, a permanent bluish-green color results.

Gelsemin gives characteristic crystalline precipitates with gold and platinum chlorides, and a well-defined crystalline hydrochloride which is readily soluble in water but difficultly so in alcohol. Its solubility in alcohol is made available in separating it from gelseminin, as the hydrochloride of the latter dissolves readily in this solvent.

Pure gelsemin appears to have a very slight toxic action and the effects of the commercial preparations are thought to be due to the gelseminin, which may be present in varying quantities.

Gelseminin

Gelseminin is the name given to an amorphous basic substance which is also obtained from gelsemium. It is apparently a mixture of two or more alkaloids.

Neither gelseminin nor its salts have been crystallized. The base gives the usual precipitates with alkaloidal reagents and resembles gelsemin in its color reactions. Physiologically it is a strong poison and much more active than gelsemin. It also produces mydriasis and mixtures of strychnin and gelseminin might on analysis be mistaken for mixtures of strychnin and belladonna.

Semperviren

This alkaloid may be obtained, according to Sayre [1] and Stevenson, by dissolving a mixture of the crude alkaloids in chloroform and completely extracting with 1 per cent hydrochloric acid. On saturating with sodium nitrate, the nitrate of semperviren is thrown out, and may be separated and crystallized from hot alcohol. The free base recovered from the salt crystallizes in reddish brown needles, soluble in chloroform and alcohol and almost insoluble in ether, benzol, and petroleum ether.

Scopoletin, $C_9H_5O_3 \cdot OCH_3$

Scopoletin is the principle of gelsemium which gives a blue fluorescence with ammonia, and is a very useful substance in analytical work for establishing the presence of the drug. It is readily soluble in chloroform from acid solutions, and on shaking the chloroform with dilute ammonia, the aqueous layer, on separation, will show a distinct blue fluorescence.

[1] J. Amer. Pharm. Ass., 1915, 1458.

Scopoletin crystallizes from alcohol in long colorless needles, melting at 204° and subliming at 140–170°. It gives an acetyl derivative, melting 177°.

This substance has been called " gelseminic " acid and has also been mistaken for æsculin, the fluorescent substance from the horse-chestnut bark which does not sublime.

Separation of the Alkaloids.—Stevenson and Sayre [1] in the reports of their researches on Gelsemium suggest a method for separating the alkaloids. The procedure in detail is as follows: the mixed alkaloids are dissolved in chloroform, which is shaken with several portions of 1 per cent hydrochloric acid, testing each portion with saturated sodium nitrate, until a fraction is obtained which gives no precipitate with the reagent. The combined acid washings are treated with a sufficient quantity of the nitrate to remove the semperviren, and the nitrate is filtered off and washed with saturated sodium nitrate and then with a small quantity of distilled water. The filtered acid solution is preserved.

The chloroform solution is then continously extracted with the 1 per cent acid until all of the alkaloids are removed, and this solution is combined with the filtered solution above mentioned. The acid solution is shaken with benzol and then with chloroform, several portions of each solvent being employed; after which it is rendered just neutral with sodium hydroxide, and evaporated to dryness at a low temperature. The residue is extracted with several small fractions of alcohol which dissolves the gelseminin hydrochloride and a portion of the gelsemin hydrochloride. The alcoholic solution is evaporated to a small volume and allowed to stand for some time when the major portion of the gelsemin hydrochloride will separate. After filtering the filtrate is mixed with sand, evaporated at a low temperature and extracted with acetone, which takes up the gelseminin hydrochloride.

The free bases can be recovered from their salts by the usual methods of alkaloidal separation.

Qualitative and Quantitative Testing.—The presence of Gelsemium as a drug either by itself or in a mixture is not difficult to establish; the scopoletin is readily detected, and following this, the identification of the bases makes the diagnosis complete. The alkaloids when alone may be identified without difficulty, the only substances for which they might be mistaken being strychnin and yohimbin, and they can be differentiated from these bases because a residue evaporated with nitric acid does not give a purple color with alcoholic potash. If, however, they occur conjointly with the bases above mentioned their identity becomes a matter of considerable difficulty, and as has already been mentioned, a mixture of strychnin and the Gelsemium bases might be mistaken for one of strych-

[1] J. Amer. Pharm. Ass., 1915, 4, 1458.

nin and the belladonna alkaloids. The reason for this is due to the fact that strychnin gives a reaction similar to Vitali's test for atropin or hyoscyamin, and the mixed Gelsemium bases produce mydriasis.

To test for scopoletin and the alkaloids, the product under examination, if a solid, should be extracted with alcohol, (if a liquid, the water should first be evaporated), the alcohol filtered off, evaporated, the residue taken up with dilute hydrochloric acid and filtered into a separator. The acid solution is then shaken out with chloroform, a portion of the solvent run into a test-tube and shaken with water containing a little ammonia; on separating the alkaline layer will show a bluish fluorescence if scopoletin is present. If it is desired to proceed further with the identity of scopoletin the chloroformic solution should be washed with water, filtered, evaporated, and the residue crystallized out of alcohol, the product obtained subjected to sublimation at about 150° C., and the melting-point of the sublimate determined. The acid solution, after the removal of the scopoletin, is then rendered alkaline, extracted with ether, then with chloroform, and portions of the residue from each extraction tested with the several oxidizing mixtures, and the gold and platinum crystalline salts examined under the microscope to observe their characteristic forms in comparison with known specimens.

In making a quantitative estimation of the amount of Gelsemium bases in a mixture, the preliminary manipulation is the same as the processes employed for identifying the alkaloids. After removing the scopoletin and other substances soluble in chloroform from an acid solution, the liquid is made alkaline and extracted with ether and chloroform, the solvents washed with water, run through a filter into a tared dish, evaporated and the residue weighed. If acetanilid and caffein have been found the acid solution must be thoroughly extracted with chloroform before rendering alkaline as these substances are both extracted from an alkaline solution.

There are no satisfactory methods known at present for the separation of gelsemin and gelseminin from codein, strychnin, ipecac, or cinchona alkaloids.

ALKALOIDS OF THE CELANDINE AND BLOODROOT

Chelidonin.
Chelerythrin.
Sanguinarin.
α-Homochelidonin.
β-Homochelidonin.
γ-Homochelidonin.
Protopin.

These alkaloids occur in the two drug plants, Chelidonium majus, garden celandine or tetterwort, and Sanguinaria canadensis, bloodroot. They also occur in Stylophorum diphyllum, Bocconia frutescans, Bocconia cordata, and Eschscholtzia Californica, all of the above plants belonging to the Papaveraceæ. Some of them are found in Adlumia cirrhosa, Fumaria officinalis, and Glaucinum corniculatum.

In addition to the above mentioned alkaloids Schlotterbeck reports the presence of other alkaloids, all of which have been summarized in the following table.

It is of special interest in our work to observe that Chelidonium does not contain sanguinarin and that Sanguinaria is free from chelidonin.

ALKALOIDS

Drug	Sanguinarin	Chelerythrin	Protopin	Chelidonin	alpha-Homochelidonin	beta-Homochelidonin	gamma-Homochelidonin
Sanguinaria	Present	Present	Present	.....	.....	Present	Present
Chelidonium	.....	Present	Present	Present	Present	Present	Present
Stylophorum	Present	.....	Present	Present	.....	.....	.....
Adlumia	.....	.....	Present	.....	.....	Present	.....
Eschscholtzia	Present	Present	Present	.....	.....	Present	Present
Bocconia	Present	Present	Present	.....	.....	Present	.....
Glaucinum	Present	Present	Present	.....	.....	.....	.....

Drug	Stylopin	Diphyllin	Adlumin	Adlumidin	Berberin	Ionidin	Glaucin
Sanguinaria	.....	.....	.....	.....	.....	.....	.....
Chelidonium	.....	.....	.....	.....	.....	.....	.....
Stylophorum	Present	Present	.....	.....	Present	.....	.....
Adlumia	.....	.....	Present	Present	.....	.....	.....
Eschscholtzia	.....	.....	.....	.....	.....	Present	.....
Bocconia	.....	.....	.....	.....	.....	.....	.....
Glaucinum	.....	.....	.....	.....	.....	.....	Present

Chelidonium majus is a perennial herb, 1 to 2 feet high, growing along fences, roadsides, and in waste places, and the entire plant is used as the drug. It was formerly official in the U. S. Pharmacopœia.

Chelidonium is a drastic purgative and is also somewhat diuretic, expectorant, and sudorific. It has been used for cancer and its juice is employed externally for corns and warts and to subdue traumatic inflammation. However, it is not a drug that is in general use and will seldom be encountered in analytical practice.

Sanguinaria canadensis is a perennial herb, about 6 inches high, growing in rich open woods.

Sanguinaria is used as a tonic, alterative, stimulant, emetic, and expectorant, but is chiefly employed as a stimulant expectorant in bronchitis, croup, and asthma. The extract of the whole drug, a concentration representing the alkaloidal constituents, and alkaloidal sanguinarin in the free state and in the form of the nitrate and sulphate are all used in the compounding of galenical preparations. Extract of Sanguinaria is mixed with the extracts of Veronica virginica (leptandra), butternut, and Hyoscyamus in liver pills; with extracts of Iris versicolor; Euonymus atropurpureus (wahoo) and Podophyllum resin; with ammonium chloride and tartar emetic with and without opiates in croup mixtures and expectorants.

Syrup Horehound compound usually contains the extracts of Sanguinaria, Inula helenium (elecampane), Aralia racemosa (spikenard), Symphytum officinalis (comfrey), Prunus serotina (wild cherry), Marrubium vulgare (horehound), and Ceanothus Americanus (Jersey tea or red root). Fluid extract wild cherry compound used for making the syrup, contains Prunus serotina, Marrubium vulgare, Veratrum viride, Lactuca canadensis (wild lettuce), and Sanguinaria. Fluid extract Lobelia compound contains Lobelia inflata, Spathyema fetida (skunk cabbage), and Sanguinaria. White pine compound often consists of Sanguinaria and morphin acetate with Pinus strobus (white pine) bark, Prunus serotina, Aralia racemosa, sassafras, and balsam poplar buds. White-pine tablets may contain opium, potassium nitrate, camphor, methyl salicylate, Sanguinaria, ipecac, Polygala senega, squills, Prunus serotina and Pinus strobus. Anodyne expectorants consist of about the same ingredients as white-pine syrup, and often contain chloroform in addition. Sanguinaria with coltsfoot, Glycyrrhiza, and demulcents are combined in throat lozenges.

The fluid extract of Sanguinaria is made with acetic acid as a menstruum, a point which should be borne in mind in case of a controversy over the presence or absence of extract of Sanguinaria in a liquid product.

With the exception of Chelidonium and Sanguinaria, the other plants containing the alkaloids under consideration have seldom been used in the composition of medicines, but their possibilities are attractive and there is no reason why they should not appear in proprietary mixtures.

Sanguinarin is generally regarded as the most important constituent from a medical point of view, though the percentage of chelerythrin in the drug is considerably greater.

Sanguinarin, $C_{20}H_{15}NO_4$

Sanguinarin crystallizes from chloroform with a melting-point of 212°. It is a white base, insoluble in alkalies, and gives intense red salts. It is probable that the molecule varies with the medium from which it crys-

tallizes and contains a portion of the solvent in its composition. It is but slightly soluble in petroleum ether, but dissolves readily in ether and chloroform. It gives precipitates with the usual alkaloidal precipitants and is indicated in the general scheme of alkaloidal analysis, when a residue, tested with Mayer's reagent, gives a red precipitate.

It gives a red color with sulphuric acid; an orange with nitric; an orange to scarlet with Erdmann's reagent; carmine to dirty brown with Froehde's; and dark green to violet brown with vanadium-sulphuric acid. The pure base dissolves in ether to a colorless solution and yields a bright-red precipitate of the hydrochloride when treated with hydrochloric acid gas.

Its salts are commercial articles and are probably impure, containing a considerable proportion of the other bases.

In the drug it is probable that the greater part of the alkaloid present is not in the form of a salt of the free base, but as a more stable compound whose salts are red in color and yield the base on hydrolysis.

Chelerythrin, $C_{20}H_{17}NO_4$

This alkaloid crystallizes from solvents with a molecule of the mother liquor from which it is freed only with difficulty. It separates from a mixture of alcohol and acetic ether in colorless crystals containing 1 molecule of alcohol, melting 203–204°; when crystallized from toluol it melts 257° and on drying at 100° it loses 10–11 per cent by weight giving off the odor of the solvent.

It has a distinct pink tinge when viewed *en masse*. When dissolved in chloroform the solvent is fluorescent, but the fluorescence seems to disappear with increased purity. It gives bright-yellow salts with acids, and those with mineral acids are but sparingly soluble in excess of acid. It is freely soluble in chloroform but only sparingly in ether.

With strong acids and Erdmann's reagent a deep-yellow color is obtained, with Froehde's reagent yellow to dirty green, and with vanadium-sulphuric acid red to violet.

A solution of chelerythrin in 95 per cent alcohol or in a mixture of alcohol and chloroform, when treated with carbon bisulphide containing iodine, gives a ruby red periodide, melting 225°.

It forms a compound with gold chloride which separates from alcohol in brown needles, melting 233° with decomposition.

Chelidonin, $C_{20}H_{19}NO_5$

Chelidonin forms crystals containing 1 molecule of water, melting 135–136°. The crystals when warmed or rubbed produce a cracking sound accompanied by the emission of light, visible in a darkened room. It is

dextrorotatory. Its hydrochloride is sparingly soluble and separates in crystals when hydrochloric acid is added to a solution of the sulphate. Gold chloride yields an orange-red precipitate which crystallizes violet-red from alcohol. The platinochloride is yellow, and melts 155°. The periodide is light red and black.

When a solution of guaiacol in sulphuric acid is sprinkled with chelidonin a carmine-red color is produced. Nitric acid added to a solution of the base in sulphuric acid gives a green color. Sulphuric acid alone produces a yellowish or orange color changing to violet; Erdmann's reagent gives a greenish yellow turning to violet; Froehde's reagent gives bluish green; vanadium-sulphuric acid gives green turning to blue green.

It forms a benzoyl derivative which melts at 217°.

Homochelidonin, $C_{21}H_{23}NO_5$

β-Homochelidonin crystallizes in clusters or rosettes of boat-shaped crystals, melting 159°. It gives a rose-pink color with sulphuric acid, intensified by vapors of nitric acid; a yellow color with nitric acid; a yellow to violet with Erdmann's reagent; Froehde's reagent produces a play of colors brown at first, then violet, blue, green and yellow; vanadium-sulphuric acid gives violet, greenish blue to brown.

It is soluble in the ordinary organic solvents. When crystallized from acetic ether it melts 169° and corresponds to γ-Homochelidonin. The form seems to depend on the solvent from which it is crystallized. Both forms give a blood-red aurochloride which crystallizes from alcohol in warty crystals, melting 187°.

The alpha-form of this alkaloid melts 182°.

Schlotterbeck's[1] description of the new alkaloids of Stylophorum diphyllum and Adlumia fungosa may be summarized as follows:

Stylopin, $C_{19}H_{19}NO_5$, melting 202°, $(\alpha)_D - 315°\ 12'$ in alcohol, is almost insoluble in hydrochloric acid and insoluble in dilute sulphuric acid, which serves as a means of separating it from chelidonin. It is soluble in glacial acetic acid, from which concentrated hydrochloric acid precipitates fine needles of the hydrochloride. The nitrate separates from aqueous solutions in clusters of needles which appear almost jelly-like *en masse*. Precipitates are obtained with the usual alkaloidal reagents, including bromin water, potassium iodide, picric acid, and bichromate.

Diphyllin, melting 216°, accompanies chelidonin and may be separated from it by fractional crystallization from ether. It gives the following color tests; nitric acid yellow, violet to carmine red, then dull green to reddish brown; Erdmann's reagent, yellowish green to bright green; Froehde's reagent, deep green, olive green to olive; Marquis' reagent, violet to wine red.

[1] J. Amer. Chem. Soc., 1902, 1; Ibid., 1903, 596.

Adlumin, melting 188°, $(\alpha)_D$+39° 88 , gives an amorphous precipitate with gold chloride which may be crystallized out of water. It is not precipitated by platinic chloride. With sulphuric acid it gives a lemon-yellow color; with nitric acid lemon to orange; Erdmann's reagent, olive green, brown to red; Marquis' reagent, light yellow to lavender.

Adlumidin, melting 234°, crystallizes in square plates usually yellow in color but white when pure. Sulphuric acid produces bright red, olive brown to pink; nitric acid orange to light yellow; Erdmann's reagent brick red, greenish to brown; Marquis' reagent, bright red. dark brown to purple.

Schlotterbeck also reports an unnamed alkaloid from Adlumia, melting 176–177°, giving with sulphuric acid light yellow; Erdmann's reagent olive, brown to wine red; and no color with Marquis' reagent.

GLAUCIN

This alkaloid crystallizes from ether in pale yellow tablets, dextrorotatory, melting 119–120°. It is a weak base and may be extracted from its acid solutions by chloroform. Its salts are fairly permanent and it is precipitated by the usual alkaloidal reagents.

Recognition of Sanguinaria and Chelidonium.—The presence of sanguinarin may be suspected in the general scheme of alkaloidal analysis when the acid solution shows a pronounced red color. Aloes will often give a red color to a solution, but this drug has an unmistakable odor which is always prominent. If the red color disappears when the solution is made alkaline and a white substance separates, insoluble in the alkaline liquid but dissolving in ether or chloroform, the worker may be reasonably sure of sanguinarin, and the evidence is further strengthened if a fluorescence is imparted to a chloroformic solution. The residue left on evaporating the solvent should be dissolved in absolute ether and treated with a stream of dry hydrochloric acid gas which will produce a precipitate of the bright red hydrochloride of sanguinarin.

Chelerythrin follows sanguinarin closely in its solvent properties, and therefore a residue obtained in medicinal analysis will generally contain both alkaloids. This fact will modify the results obtained in performing color tests and unusual results must not be taken as negative indications. The color tests reported under the descriptions of the individual bases have been taken from the reports of the researches on the respective substances, but they must not be considered as absolutely correct. The alkaloids of this group have not been subjected to the same degree of careful investigation as those of some of the other drugs and until further research has been performed much of the data must be taken with reserve.

The separation of sanguinarin from chelerythrin has been effected by

Kozniewski [1] who took advantage of the difference in solubility of their sulphates, but such a procedure is of little use in our work owing to the limited amount of material available in any one sample.

If the analyst is presented with a cough lozenge which presumably contains a large percentage of demulcent substances, and which he wishes to test for sanguinarin, the simplest procedure consists in grinding as many lozenges as can be spared and extracting them directly with ether. The ether solution will contain the bases with but little contaminating material and the pure alkaloids can then be extracted with dilute sulphuric acid and recovered from the acid solution by adding ammonia and shaking out with ether or chloroform.

The mixtures containing sanguinarin are of such a nature that the identity of the alkaloid is not difficult to determine.

Kozniewski, Anz. Akad. Wiss. Krakan, 1910. Reihe, A. 235, J. Chem. Soc., Abst., 1910, 874.

CHAPTER VIII

ALKALOIDS WHICH PROBABLY CONTAIN A PYRIDIN NUCLEUS

THE STRYCHNOS ALKALOIDS

Strychnin, $C_{21}H_{22}N_2O_2$.
Brucin, $C_{23}H_{26}N_2O_4$.
Strychnicin.
Tubocurarin, $C_{19}H_{21}NO_4$.
Curin, $C_{18}H_{19}NO_3$.
Curarin, $C_{19}H_{26}N_2O$.
Protocurin, $C_{20}H_{23}NO_3$.
Protocuridin, $C_{19}H_{21}NO_3$.
Protocurarin, $C_{19}H_{23}NO_2$.

Strychnin is found in the seed and pulp of Nux Vomica, Strychnos Nux Vomica (Loganiaceæ), in the bark of the same plant "false Angostura bark," and in the seeds of Strychnos ignatia "St. Ignatius Beans." It also occurs in the root and wood of S. columbrina L., snakewood tree; in the seeds and roots of S. tieute "deadly upas-tree," the root extract of which is employed in the preparation of a poison known as Upas Tieute or Upas Radja; and in the bark of S. malaccensis, known as Hoang-Nan.

Brucin accompanies strychnin in all the above plants, but the seeds of S. rheedii contain brucin alone, and according to Bruhl S. ligustrina contains 2.26 per cent brucin, but no strychnin. Strychnicin is claimed by Boorsina to occur in the leaves of S. Nux Vomica.

The other alkaloids are found in Curare, the dark resinous extract of several species of Strychnos, particularly of S. toxifera and S. castetuaca.

The pulp in which the Nux Vomica seeds are imbedded contains when dry about 5 per cent of loganin, a crystalline glucoside.

The extreme bitterness of the Strychnos bark, its twisted appearance, the impossibility of separating it into thin layers, and the blood-red coloration produced on applying nitric acid to the internal coat are characters by which it is easy to distinguish it from the true Angostura bark.

The Nux Vomica of commerce comes principally from India, Ceylon, Cochin-China, and Northern Australia. The Ceylon seeds contain from

4.4 to 5.4 per cent of the mixed alkaloids, those from Bombay 3.2 per cent, from Cochin-China 3 per cent, from Madras 2.75 per cent. The amount of strychnin is a little less than half. The alkaloids are combined with igasuric (" strychnic ") acid, which appears to be identical with chlorogenic acid.

Preparations containing Nux Vomica or its alkaloids are used for general tonic purposes, and the principles often occur in remedies for neuralgia, impotence, neurasthenia, constipation, and cardiac troubles. Ignatia and Hoang-Nan containing the same constituents as Nux Vomica, are used for the same purposes though to a very limited extent compared with Nux Vomica.

Pills and tablets of Nux Vomica or of strychnin are many and varied as to their composition. The anti-constipation formulas employ aloes and strychnin, or aloin, belladonna, and strychnin, combined with one or more of the following: Cascara, ipecac, rhubarb, Podophyllum, Capsicum, Hyoscyamus, gentian, and jalap. Anti-malarial compounds contain strychnin with iron, quinin, arsenic, aloes, Hyoscyamus, Capsicum, or bismuth subnitrate. With ipecac, belladonna, colocynth, mercury, sodium bicarbonate, often with pepsin and sometimes with iron and bismuth subnitrate it will be found in anti-dyspeptic mixtures. Carminatives contain strychnin with ipecac, gentian, and black pepper. With Cactus grandiflorus, spartein, digitalin, nitroglycerin, and strophanthin, it enters into the composition of heart tonics.

Combinations of strychnin, irisin, Podophyllum, and Hyoscyamus are not uncommon. Iron, arsenic, and strychnin is a common formula, and this is often combined with quinin salts, with ipecac, aloes, gentian, cascara, creosote, and various hypophosphites, the different combinations being used as tonics. Neuralgics will contain strychnin, aconitin, quinin, and arsenic occasionally, with the addition of morphin, zinc phosphide, and Cannabis sativa. The so-called nerve tonics, aphrodisiacs, " restorers " and the like, contain strychnin in combination with phosphorus, cantharides, zinc salts, iron compounds, often with aloes, quinin, damiana, and gold and sodium chloride. Certain " sedatives " contain strychnin, valerianates or valerian, cocain, codein, arsenic, Cannabis sativa, and iron salts.

Among the liquid products strychnin will be found in a number of combinations usually in the form of elixirs, the more important being general tonics, aphrodisiacs, heart tonics, and digestants. These will contain in addition to strychnin, various proportions of Cinchona alkaloids, iron salts, bismuth, and ammonium citrate, pepsin, aloin, Podophyllum, and belladonna; phosphorus and damiana; and Digitalis, Strophanthus, and nitro-glycerin. The " Hypophosphite " and " Phosphate " class of syrups nearly always contain strychnin combined with phosphates or hypo-

phosphites of potassium, sodium, magnesium, calcium, manganese, iron, quinin, and free phosphoric acid.

Capsules of strychnin with cresote, codliver oil, atropin, and arsenous acid are used medicinally.

Malt products often contain strychnin in combination with quinin.

Preparations of ignatia are few, but it occurs in a pill and tablet formula used as an anti-neuralgic, where it is combined with opium, Hyoscyamus, belladonna, Conium, stramonium, aconite, and Cannabis sativa. It is also sold in liquid and tablet form combined with phosphorus, Cinchona, gentian, Calumba, and Nux Vomica.

The curare alkaloids are used occasionally for anti-tetanics and nerve stimulants.

Strychnin

Strychnin occurs in the form of colorless, transparent, prismatic crystals or a white crystalline powder, anhydrous, odorless, permanent in the air, and having an intensely bitter taste. It is a tertiary, monacid base, extremely poisonous, and should be handled with caution.

From the results of experiments conducted by Claus and Glassner [1] it would appear that the strychnin of commerce is not always of the same composition, in some instances corresponding to the formula $C_{22}H_{22}N_2O_2$ and in others to $C_{21}H_{22}N_2O_2$. It was apparent from this work that commercial strychnin probably contained homostrychnin, $C_{22}H_{24}N_2O_2$.

The melting-point is variously given from 265° to 269°. It will distill without decomposition at a pressure of 5 mm.

It is readily soluble in chloroform and hot alcohol and fairly soluble in benzol and amyl alcohol, much less in ether and with difficulty in water and petroleum ether. The latter solvent will, however, remove strychnin from a solution made alkaline with ammonia.

Strychnin solutions are lævogyrate and alkaline in reaction.

Concentrated sulphuric acid, Erdmann's and Froehde's reagents, dissolve strychnin without color. Its solution in nitric acid becomes yellow. It is readily soluble in dilute acids. On heating with concentrated sulphuric acid, at 100°, a sulphonic acid of strychnin is produced which gives very insoluble precipitates with the alkali and alkaline earth metals and also with lead and copper.

Solutions of strychnin are precipitated by ammonia and the alkalies, but not by sodium bicarbonate. Strychnin is not very soluble in solutions of the alkalies, but dissolves somewhat easily in ammonia.

Strychnin forms a number of well-defined salts, some of which are readily soluble in water, while others are very insoluble. Most of the

[1] Berichte, 14, 773.

salts are soluble in alcohol but are insoluble in the other ordinary organic solvents. The hydrochloride, hydrobromide, nitrate, sulphate, acid sulphate, and acetate, dissolve in water without great difficulty. The hydriodide is only sparingly soluble, while very insoluble and characteristic precipitates are obtained with potassium chromate, ferrocyanide and ferricyanide, mercuric chloride, sodium phospho-molybdate and phosphotungstate, potassium bismuth iodide, potassium-mercuric iodide, iodine, platinic and gold chlorides, tannic and picric acids; and the varying solubilities of the isomeric salts have been of great value in the development of the chemistry of tartaric acid and other acids having stereoisomeric modifications. It also forms a compound with sulphide of hydrogen when treated in alcoholic solutions with this reagent or with alcoholic yellow ammonia sulphide.

The precipitate obtained with potassium-bismuth iodide is one of the most insoluble combinations, closely followed by the chromate, ferrocyanide, mercurochloride, phosphotungstate, phosphomolybdate, and mercuroiodide. The reactions with ferrocyanide and chromate are of value in separating strychnin from brucin, and the ferrocyanide reaction has been employed quantitatively.

The precipitate formed with a solution of iodine in alcohol resembles herepathite, the product of similar nature given with quinin. Strychnin is removed from an aqueous solution by animal charcoal.

The color reactions of strychnin are extremely sensitive and important as a means of identifying the alkaloid. When dissolved in concentrated sulphuric acid and treated in the cold with an oxidizing agent a purple color develops, more or less fleeting, depending on the quantity of the alkaloid and the particular agent employed, and which finally becomes pale cherry-red. Potassium bichromate probably has been employed as an oxidizing agent to a greater extent than any other. Allen prefers manganese dioxide, and other substances, ammonium vanadate, cerosoceric oxide, potassium ferricyanide have been highly recommended. The play of colors depends on the quantity of material present. With sufficient of the alkaloid, the full change from blue to purple, purplish-red, cherry red, and finally yellow, will be noted, but when the amount is small a purple changing rapidly to yellow will be the only marked characteristic. When the quantity is very small it is advisable to dissolve the oxidizing agent in the acid before adding the latter to the residue under examination.

This reaction, while very characteristic of strychnin, is unfortunately given in similar manner by other drug products which are extracted from alkaline solutions under the same conditions that strychnin would be withdrawn, and while in large amount there might be differences in the reaction sufficient to show wherein the product was not strychnin, there would always be a doubt, especially in forensic work, unless fully substantiated

by other tests, and when the quantity was small the difficulty of differentiating would be well nigh impossible.

Some substances give colors with sulphuric acid alone, codliver oil being one which, when pure, produces a beautiful display of shades, from purple through crimson, to brown. Certain glucosides and other principles produce colors, but most of them are removed from acid solution by immiscible solvents. Anilin is stated to give with sulphuric acid and oxidizing agents a green color, changing to blue and eventually becoming black. Allen states that colocynth resin gives a very similar reaction to strychnin, but is removed by agitating the acidulated solution with benzol or ether. The writer found, however, that when working with an extract of colocynth, sufficient material remained in solution after previously shaking out the acid liquid with immiscible solvents, to appear later in the residues obtained by shaking out the alkaline solution and give a purple tint with sulphuric acid and oxidizing agents. The reaction in this case, however, in no way resembled that obtained with strychnin, for a dirty color first appeared and after several minutes a purple shade was apparent in thin layers.

It has been shown that residues obtained by shaking out alkaline solutions of the following drugs with immiscible solvents give a purple reaction with sulphuric acid and bichromate, namely, Gelsemium, Hydrastis, opium, Sanguinaria, and yohimbé. The similarity in the reactions of strychnin and yohimbin is of interest, as the drug containing the latter alkaloid has of late been exploited as a remedial agent for the same purposes that strychnin has been used. It has been claimed to possess aphrodisiac properties and might be suspected in mixtures advertised for tonics and the like. When working with small quantities the reactions are so much alike that one could form no conclusion as to which alkaloid was present. In larger amount the yohimbin gives a purple, changing to reddish and then to olive green and in still larger amount the color is first an indigo blue. The reaction with ammonium vanadate, however, is so nearly identical with that given by strychnin that no distinction can be drawn with any safety. However, yohimbin forms very few salts which have any characteristic form under the microscope, while those given by strychnin are well defined and can be distinguished readily, and furthermore its physiological action is different. There is little danger of confusing strychnin with the principle of colocynth, which gives the purple color with sulphuric acid and bichromate, and as regards the alkaloids of Hydrastis, Gelsemium, and Sanguinaria, which act similarly, none gives the purple color with nitric acid and alcoholic potash subsequently described, and there are a number of distinctive characteristic reactions for these substances which are fully described under their respective headings. With ammonium vanadate, berberin gives a red, soon chang-

ing to plum-color, and gelseminin a magenta, changing to blue green. The purple color given by the opium alkaloids would hardly be mistaken for that given by strychnin, as it is very lasting. It was found on investigation that narcein and papaverin were the two alkaloids giving the purple tint, no similar reaction being obtained with thebain, narcotin, codein, or morphin. Curarin gives virtually the same color reaction as strychnin, and a ptomain has been described giving a similar oxidation test.

In small proportions brucin exercises no injurious influence on the oxidation test for strychnin, but when much is present it interferes in a marked manner. Hence it is safest to separate the strychnin first as chromate or ferrocyanide by precipitation and after filtering to examine the solution for brucin. Another method directs the solution of the substance in concentrated sulphuric acid, adding a trace of nitric acid or potassium nitrate and waiting until the red color changes to yellow, when a crystal of potassium bichromate will give the characteristic strychnin reaction.

The writer has obtained good results by shaking out the alkaline solution two or three times with petroleum ether and testing the residue left on evaporation of the solvent, for strychnin. Then on shaking out with chloroform the brucin will be removed and may be identified by testing the residue on evaporation.

Strychnin when evaporated with concentrated nitric acid leaves a yellowish residue which becomes a beautiful purple on treatment with a few drops of alcoholic potash, the reaction being very similar to that given by atropin. In connection with this test, it is of interest to note that yohimbin gives the same reaction. When working with extract of Nux Vomica it was found that only the alkaloidal portion removed by petroleum ether would give the purple color on adding the alcoholic potash, for the red color produced by the nitric acid on the brucin masked the purple tint given by the strychnin. Extracts from coca leaf and Colchicum have been found to give purple colorations when this test was applied.

Buchbinder has developed a color reaction which is very characteristic and little affected by impurities. The reaction is based on a test first published by Malaquin and then studied by Denigès. Zinc amalgam is prepared by treating granular zinc with a little concentrated hydrochloric acid to clear the surface. The acid is poured off and the metal covered with 1 per cent solution of tartar emetic, shaking occasionally during one hour, 1 mil of saturated solution of mercuric chloride is added for every gram of zinc, followed by a few drops of concentrated hydrochloric acid, and after one-half hour the solution is poured off, the zinc washed and dried. To the dry alkaloid or to 0.5 mil of an aqueous solution, 0.5–1 gram of the zinc amalgam is added followed by 0.5 mil con-

centrated hydrochloric acid. After ten to twenty minutes the solution is poured from the zinc, a few drops of 0.02 per cent potassium ferrocyanide solution added, when a color varying from pink to rose red is produced.

There are a number of other color reactions reported for strychnin, and their use subsequent to the others above mentioned are of value in differentiating strychnin from those substances which give the oxidation tests.

When treated with nitric acid and potassium chlorate after warming, an intense scarlet coloration is produced. This is changed to brown on adding ammonia, and on evaporation to dryness a dark green residue is left, soluble in water with a green color, changed to orange-brown by caustic potash and becoming green again on adding nitric acid.

Zinc chloride gives a scarlet reaction with strychnin. A dry residue is moistened with a solution of 1 gram of melted zinc chloride in 30 mils of water and dried again. Brucin prevents the formation of the scarlet color, a dirty-yellow color developing. Veratrin will also give a red color and delphinin a red-brown.

The appearance of the salts of strychnin under the microscope furnishes one of the most conclusive means for identifying this alkaloid.

Gelseminin, which also gives an oxidation reaction similar to strychnin, has the same physiological action on the frog.

Brucin

Brucin is very similar to strychnin, and like the latter is a monacid, tertiary base. It contains two methoxyl groups, while strychnin contains none, the difference in the molecular weight of the two bodies corresponding to the difference in their two methoxyl groups. On this account and from other data deduced from a study of the oxidation products, it appears that brucin is the dimethoxy-derivative of strychnin.

Commercially it may be prepared by taking advantage of the insolubility of its oxalate in absolute alcohol, the oxalate of strychnin being dissolved; or the mixed alkaloids may be treated with cold absolute alcohol or acetone which dissolves the brucin readily, leaving most of the strychnin behind. The commercial product has been claimed to consist of two homologous alkaloids.

Brucin crystallizes from water with two or four molecules of water, ordinarily four, forming monoclinic prisms or shining leaflets, white, odorless, and very bitter. From alcohol it is stated to crystallize with two molecules of water. The crystals melt in their water of crystallization when heated a little over 100° C. and the anhydrous base dried at 150° melts at 178° C. It is lævorotatory.

It is much more soluble in water and alcohol than strychnin, dissolves readily in chloroform and benzol, somewhat soluble in ether. Allen claims that it will dissolve in 120 parts of petroleum ether, while the writer has found that in shaking out an alkaline solution of the mixed bases some of the strychnin will be removed by the petroleum ether, leaving the brucin behind. This, however, may be due to the greater solubility of the brucin in water. It is much less poisonous than strychnin, the physiological activity of the latter having been variously estimated as being 10 to 38 greater than that of brucin. It is a weaker base than strychnin, but forms a number of well-defined salts. The hydrochloride, hydroiodide, nitrate, and sulphate are all soluble in water. The chromate and ferrocyanide are much more soluble than the corresponding strychnin compounds and are of value in effecting a separation of the two alkaloids. The ferricyanide and hydrochloroplatinate are characteristic compounds showing well-developed forms under the microscope, and heavy precipitates are obtained with iodine-potassium iodide, potassium mercuric iodide, potassium bismuthous iodide, tannic and phosphomolybdic acids. When a solution of brucin in absolute alcohol is treated with alcoholic ammonium sulphide containing dissolved sulphur a product is formed having the composition $(C_{22}H_{26}N_2O_4)_2H_2S_8 2H_2O$, which may be obtained as orange-red crystals.

Brucin is of value in separating racemic acids as it forms salts having different solubilities.

Brucin does not resemble strychnin in its action with sulphuric acid and oxidizing agents. Pure sulphuric acid dissolves it without color, while the presence of a trace of nitric acid produces a reddish tint.

On adding concentrated nitric acid in the cold to a brucin residue a scarlet or blood-red coloration is produced which on heating changes to yellowish red and finally to yellow. On adding a few drops of freshly prepared dilute stannous chloride solution, an intense violet color will appear, which changes again to yellow or red on heating, and again reappears on the addition of more stannous chloride. To perform this test successfully the amount of nitric acid used should be small. Mauch claims to obtain excellent results by a modification of this test in which the brucin is dissolved in a 60 per cent aqueous solution of chloral hydrate. A small quantity of the mixture, about 0.5 mil, is placed in a test-tube and a few drops of nitric acid added and the whole shaken and poured carefully onto the surface of about 2 mils of concentrated sulphuric acid, when a yellowish-red or deep red zone, depending on the quantity of brucin present, will develop. As soon as the upper layer becomes yellow, stannous chloride is cautiously added by means of a pipette in order to form a top layer and on the dividing line an intense violet zone will form. The stannous chloride solution recommended consists of 1 part

stannous chloride in 9 parts hydrochloric acid having a specific gravity of 1.12.

The orange color produced by adding nitric acid to morphin remains unchanged on the addition of stannous chloride.

If the cold nitric acid be added to solid brucin so as to develop the color, and the mixture then largely diluted with water, a body called kakotelin separates in yellow flocks. The filtered liquid, after neutralization by ammonia, gives a precipitate of calcium oxalate on treatment with calcium chloride. The precipitated kakotelin may be dissolved in dilute hydrochloric acid and crystallized therefrom in orange-red or yellow scales. Its composition is $C_{20}H_{22}(NO_2)_2N_2O_5$.

Potassium bichromate throws down from solutions of brucin salts a yellow precipitate of brucin chromate which is insoluble in acetic acid, but soluble in nitric acid with a red color.

Mercurous nitrate added to an aqueous solution of a brucin salt produces no change, but on warming a carmine color appears.

A residue obtained on evaporating a solution of brucin in concentrated nitric acid will change to grass green on the application of fumes of ammonia gas, and the green product dissolves in hydrogen peroxide with formation of a violet color. This test, however, is not delicate in the presence of strychnin.

The red coloration produced by brucin in the presence of nitric acid is of value for the detection of nitric acid or nitrates in water. A drop of the water in question is treated with several drops of brucin solution in water (1–2000), several drops of hydrochloric acid then added and shaken after the addition of a few mils of sulphuric acid. In the presence of a nitrate a rose to a red color develops, quickly changing to yellow.

Brucin forms a number of well-defined derivatives.

On passing nitrogen trioxide into an alcoholic solution of the alkaloid, brucin nitrate at first separates, but again dissolves, forming a red solution, from which dinitrobrucin, $C_{23}H_{24}(NO_2)_2N_2O_4$, separates as a heavy, granular, blood-red precipitate. By washing with alcohol and ether, it is obtained as an amorphous, velvety vermilion-colored powder, easily soluble in water, sparingly soluble in alcohol, and insoluble in ether.

Separation of Strychnin for Purposes of Identification.—If the substance is a solid, extract with 95 per cent alcohol; if a liquid, first evaporate the water, and then extract with the alcohol. Evaporate the solution until the alcohol has been driven off. Digest the residue with normal sulphuric acid and filter into a separator; add ammonia in excess and shake out three times with Prolius mixture. Filter the combined portions of the solvent and evaporate over the steam-bath. Dissolve the residue in normal sulphuric acid, pour the solution into a separator and shake out first with chloroform and then with low-boiling 40–50° petro-

leum ether, discarding the solvents. Add excess of ammonia to the aqueous solution and shake out three times with petroleum ether. Collect the solvent in another separator, wash with water, filter, and evaporate over the steam-bath. The petroleum-ether residue yields a strychnin of great purity, practically free from brucin.

Quantitative Determination of Strychnin and Brucin.—If a medicinal agent contains no other alkaloid-bearing drug than Nux Vomica, nor any alkaloid except strychnin the determination of the amount present is attended with little trouble other than attention to details in the manipulation and possibly special treatments depending on the other ingredients.

If the product contains but a small amount of solid material and no gum or emulsifying substances, the alkaloids may be removed by shaking out the ammoniacal solution with chloroform at least three times after first driving off any alcohol. If both strychnin and brucin are present the two may be separated and determined by the nitric acid process as described in the assay of Nux Vomica. This method is simpler and probably more accurate than the ferrocyanide process recommended by earlier workers.

If the residue left on evaporating the chloroform contains no brucin it should be dissolved again in dilute sulphuric acid, the solution shaken out with ether and chloroform, then rendered ammoniacal and the strychnin removed by chloroform.

The principal alkaloidal drugs which are used in combination with Nux Vomica include belladonna, coca, ipecac, Conium, and Stramonium, the two latter but seldom. The same drugs will be found in products containing strychnin alkaloid and in addition strychnin may be combined with quinin, morphin, aconitin, hyoscyamin, and spartein.

The Nux Vomica alkaloids may be separated from the coca bases by dissolving the weighed residue of both in dilute hydrochloric acid and subjecting the mixture to the heat of the steam-bath for four hours in a digestion flask. The solution should then be shaken out with ether and chloroform, ammonia added in excess and the strychnin and brucin removed by chloroform.

Strychnin and brucin may be separated from atropin by precipitating the former with platinic chloride. The precipitate should be washed with platinic chloride, and the strychnin and brucin subsequently recovered from the same. The atropin may be separated from the filtrate by adding ammonia, filtering, and shaking out with chloroform. The same principles may be employed in separating a mixture of the alkaloids of Nux Vomica, coca, and belladonna.

Determination of Strychnin in Tablet Triturates.—Transfer a carefully weighed amount, .3000 gram, of the powder to a 200-mil Squibb separator and moisten with 5 mils water. Add 1 mil stronger ammonia

water. Agitate with 25 mils chloroform and allow to stand until separation is complete. Draw off the chloroform into a second separator and repeat the agitation twice more with 25-mil portions of the solvent. After combining all of the fractions, wash the combined chloroformic solutions by agitation with 10 mils of distilled water and allow to stand fifteen minutes. Introduce a pledget of absorbent cotton into the stem of the separator and run off the chloroform into a tared dish, but do not allow the wash water to enter the orifice of the stop-cock. Add 10 mils chloroform and when the water has entirely risen to the surface, run off the chloroform into the tared beaker. Wash off the outer surface of the stem of the separator with a little chloroform and then evaporate over a steam water-bath, using a fan or blower and removing from the bath as the last portions evaporate to avoid decrepitation. Dry at 100° to a constant weight and weigh as strychnin. The weight of strychnin may be checked by dissolving the residue in neutral alcohol, adding an excess of N/10 sulphuric acid and titrating back with N/50 potassium hydroxide.

Strychnin to Strychnin Sulphate 1.2815 according to U. S. P.

One mil N/10 sulphuric acid is equivalent to 0.03342 gram of strychnin and 0.04282 gram strychnin sulphate, crystalline ($5H_2O$).

In some cases, especially where the solvent dissolves substances from the tablet other than strychnin, it will be necessary to adopt the following modification of the above:

The procedure is followed down to but not including the washing of the combined chloroform extract with water. Discard the alkaline solution remaining in the first separator. Treat the combined chloroform extracts with 10 mils N/1 sulphuric acid and agitate. Allow to stand until separation is complete and collect the chloroform in a second separator. Repeat the extraction with N/1 sulphuric acid twice more, discard the chloroform and combine the acid fractions. Add stronger ammonia in excess, cool, and shake out with three successive portions of 25 mils each of chloroform, finally combining all fractions. Wash the combined chloroform solutions by agitation with 10 mils of distilled water and allow to stand fifteen minutes. Draw off the solvent through a pledget of absorbent cotton into a tared dish and finish the determination precisely as described.

It has been the experience of the author that, in conducting assays of strychnin, reliance should be placed on a gravimetric estimation, and not on one obtained volumetrically.

Determination of Strychnin in Liquid Products.—The method herein described is applicable to elixirs of iron and strychnin, quinin and other alkaloids being absent.

Take a 50-mil volumetric flask, fill to mark with sample and weigh. Pour into an evaporating dish, washing out the flask with water and evap-

orate off alcohol. Transfer to an 8-ounce Squibb separator. Add excess of ammonia. Agitate with 25 mils chloroform and allow to stand until separation is complete. Draw off the chloroform into a second separator and repeat the agitation twice more with 25-mil portions of the solvent. After combining all of the fractions, wash the combined chloroformic solutions by agitation with 10 mils of distilled water and allow to stand fifteen minutes. Introduce a pledget of absorbent cotton into the stem of the separator and run off the chloroform into a tared dish, but do not allow the wash water to enter the orifice of the stop-cock. Add 10 mils chloroform and when the water has entirely risen to the surface, run off the chloroform into the tared beaker. Wash off the outer surface of the stem of the separator with a little chloroform and then evaporate over a steam water-bath, using a fan or blower and removing from the bath as the last portions evaporate to avoid decrepitation. Dry at 100° to a constant weight and weigh as strychnin. Calculations as above.

Quantitative Estimation of Strychnin in Presence of Quinin (G. N. Watson [1]**).**—Dissolve .05 to .1 gram of the mixed alkaloids (depending on the amount of strychnin present) in 5 mils alcohol-hydrochloric acid mixture (9 parts alcohol 95 per cent and 1 part dilute hydrochloric acid), add 20 per cent solution of platinic chloride, drop by drop, while slightly agitating the mixture until the precipitation is complete. Add 5 mils more of the solvent, cover with a watch-glass, set aside for one hour filter onto a Gooch, wash with alcohol, dry at 100° C. for fifteen minutes, cool and weigh. If the proportion of quinin is large, it will be necessary to add from 5 to 15 mils more of the solvent before filtering. It will also be necessary to decompose the precipitate with sodium hydroxide, dissolve out the strychnin with chloroform, evaporate, dissolve the residue in the alcohol-hydrochloric acid mixture, and repeat the precipitation with platinic chloride.

The chlorplatinate of strychnin contains 62 per cent of alkaloid.

The quinin can be determined in the filtrate and washings by adding alkali, agitating with ether, separating, evaporating the ether, and weighing the residue.

To make this separation applicable to elixirs containing strychnin and quinin, a measured quantity of the sample should be made alkaline with ammonia and the alkaloids removed by means of Prolius mixture. After separating and evaporating the solvent the residue is subjected to the above procedure.

Separation and Determination of Strychnin and Quinin (H. E. Buchbinder).—This procedure is applicable for determining small quantities of strychnin in the presence of comparatively large quantities of quinin

[1] Journ. Amer. Pharm. Ass., 1915, 935.

and can be used for assaying the elixirs of iron, quinin, and strychnin of the National Formulary.

Take 50 mils of the sample, carefully measured and weighed. Transfer to a separator, dilute with water, and render ammoniacal. Shake out six times with ether-chloroform mixture (3–1). The extracts are combined, and the bulk of the solvent dispelled, the remainder being collected in a tared beaker and the container used for evaporation, carefully washed free from all alkaloid with the ether-chloroform mixture. Expel the solvent and dry at 100–105°. Cool and weigh as combined alkaloids.

Dissolve the residue in 10 mils of alcohol, add 4 mils N/2 hydrochloric acid or sufficient to render the solution red to methyl red, with 1 mil N acid in excess for every 20 mils of the aqueous solution as finally made up (see below). (The volume of the solution is to be regulated by the amount of quinin present.) Add 36 mils water. (If there is more than six grams of total alkaloid add about seven mils of water for every additional gram of quinin.) Add 3 mils saturated solution potassium oxalate. (Use 1 mil for every gram or less of quinin and 1 mil for every 20 mils of aqueous solution.) Stir and when precipitate has settled, place on steam-bath and heat to boiling temperature. Add a little alcohol to take up the undissolved precipitate at the boiling-point. Remove from bath, allow to cool spontaneously, breaking up surface film from time to time. Allow to stand at least five hours. Filter with vacuum, preserving filtrate, and collect crystals on a plug of cotton inserted in the stem of an ordinary funnel. Wash six or seven times with cold water. Concentrate filtrate and washings until all of the alcohol has been removed. Cool. Should there be a second crop of crystals, heat to redissolve, add $\frac{1}{2}$ to 1 mil N/1 hydrochloric acid and repeat above procedure.

Adjust in a flask to a 5–7 per cent sulphuric acid solution at 50 mils, using water and dilute sulphuric acid. Add 4 mils potassium ferrocyanide solution 10 per cent, drop by drop, stirring constantly. Allow mixture to stand overnight. Filter and wash twice with 5-mil portions of 5 per cent sulphuric acid containing a few drops of potassium ferrocyanide. (Do not attempt to remove all of the precipitate from the flask.) Transfer precipitate on filter to a small separator using a fine jet of water. To the flask add 5 mils strong ammonia and 15 mils chloroform. Agitate and pour into separator. Rinse and agitate flask twice more with 10-mil portions of chloroform, pouring each into separator. Agitate the separator, collect chloroform in another separator and repeat the extraction twice more. Combine all of the chloroform extracts, wash with water, filter into a tared beaker through a plug of absorbent cotton in the stem of the separator, wash out separator and cotton with a portion of chloroform, evaporate solvent, dry at 100–105° and weigh.

ALKALOIDS OF PEGANUM HARMALA

Harmin, $C_{13}H_{12}N_2O$.
Harmalin, $C_{13}H_{14}N_2O$.
Harmalol, $C_{12}H_{12}N_2O$.

These alkaloids occur in the seeds of Peganum harmala (Zygophyllaceæ), an herbaceous plant growing in Southern Europe and parts of Asia. The seeds are called Harmal or Ispanol and in India are used as a genito-urinary stimulant, anthelmintic, and emmenagogue. They are also narcotic and are used for the same purposes as Cannabis sativa. These alkaloids or preparations containing the drug are not used to any great extent.

Extract of P. harmala is used as a red dye.

Harmin

Harmin crystallizes from alcohol in needles, melting 256–257°, inactive, subliming unchanged and sparingly soluble in water, alcohol, and ether. Its salts are colorless and show an indigo-blue fluorescence in aqueous solution. It dissolves in concentrated sulphuric acid to a greenish fluorescent solution.

Harmin contains an OCH_3 group which may be eliminated by HCl or HI, yielding harmol, a phenol. The latter crystallizes in needles melting 321°.

Harmalin

This alkaloid crystallizes from methyl alcohol in plates or needles, melting with decomposition 238°. It is optically inactive, almost insoluble in water, sparingly soluble in alcohol and ether, and may be precipitated from an alcoholic solution by ether. Its salts are yellow and in aqueous solution, show a blue fluorescence, but the solution in concentrated sulphuric acid does not fluoresce.

When dissolved in cold pyridin and treated with acetyl chloride, harmalin forms an acetyl derivative which crystallizes from alcohol in needles melting 204–205° C.

Harmalin contains an OCH_3 group which is eliminated by HCl, yielding harmalol, a phenolic alkaloid, which crystallizes in red needles, melting 212°. It is probable that the latter substance exists to a certain extent in the plant. Harmalol dissolves in water with considerable difficulty, yielding a yellowish solution with fluorescence. Acids or alkalies destroy the fluorescence.

ALKALOIDS OF THE ACONITE GROUP

Aconitin, $C_{34}H_{47}NO_{11}$.
Japaconitin, $C_{34}H_{49}NO_{11}$.
Indaconitin, $C_{34}H_{47}NO_{10}$.
Pseudaconitin, $C_{36}H_{51}NO_{12}$.
Bikhaconitin, $C_{36}H_{51}NO_{11}$.
Jesaconitin, $C_{40}H_{51}NO_{12}$.
Lycaconitin, $C_{27}H_{34}N_2O_6 \cdot 2H_2O$.
Myoctonin.
Lapaconitin, $C_{34}H_{48}N_2O_8$.
Septentrionalin, $C_{31}H_{48}N_2O_9$.
Cynoctonin, $C_{36}H_{54}N_2O_{13}$.
Atisin, $C_{22}H_{31}NO_2$.
Palmatisin.

Most of the different species of Aconitum (family Ranunculaceæ) contain one or more characteristic alkaloids, some extremely poisonous, and others with feeble toxic properties, and from a close study of some of the more commonly known of these plants, it appears that each is characterized by a distinct alkaloid. The alkaloids occur in all parts of the plants and in some pharmacopœias both the leaves and the root are official, though in ours, only the root is recognized. The plant designated in the U. S. Pharmacopœia is A. napellus. The root is about 2–4 inches long and $\frac{2}{3}$ to 1 inch in diameter at the widest portion, being tuberous and of irregular conical form, brownish externally, white or light brown and starchy within. It is biennial and normally paired, one tuber of each pair when mature bearing a flowering stem, the other having a bud. The parent tubers may be distinguished by the scar of the stem, and the spongy or hollow condition of the root. The fresh leaves have a faint narcotic odor, and a bitterish herbaceous taste, afterwards acrid with a feeling of numbness and tingling on the inside of the lips, tongue, and fauces which may last an hour or more. The dried leaves produce the same sensation. The root has a sweetish taste at first, but afterwards the same effect as the leaves.

Of late years much "Japanese Aconite" has been coming into the markets of the United States. The species yielding this drug is A. fisheri. The drug usually consists of mother (with stem bases) and daughter tubers (with buds), which may be distinguished from those of the official aconite by their much smaller size and weight, less wrinkled, and not twisted appearance, more or less short conical shape, generally more mealy condition due to starch, and microscopically by the different arrangement of the fibro-vascular bundles, which is usually not so markedly star shaped.

Adulteration of aconite with Imperatoria ostruthium, masterwort, is reported.

Commercial aconitin may consist of a mixture of one or more alkaloids, depending on the drug from which the extraction was made. The whole question of aconite analysis has been the subject of considerable controversy, but Dunston and his collaborators have done a great service in sifting out the data and showing the source of the various aconitins.

A. napellus contains aconitin.
A. fischeri contains japaconitin.
A. chasmanthum contains indaconitin.
A. dinorrhizum contains pseudaconiton.
A. spicatum contains bikhaconitin.
A. japonicum contains jesaconitin.
A. vulparia or A. lycoctonum contains lycaconitin and myoctonin.
A. lycoconum or A. septentrionale contains lapaconitin and septentrionalin.
A. hetrophyllum contains atisin.
A. palmatum contains palmatisin.

In addition to these there are a number of aconites which contain bases as yet little studied.

Aconitic acid is apparently a constant constituent of aconite and it is probable that the alkaloids are in part combined in the plant.

The interest of the drug analyst will be chiefly confined to the chemistry of A. napellus, though, as indicated above, the commercial alkaloids may consist of one or many individuals of the aconite group. These alkaloids are extremely poisonous, their employment as remedial agents is limited, and they will be encountered only rarely in the general run of drug work.

Aconite is a cardiac and nervous sedative, and is used in fevers as a diaphoretic, in cardiac hypertrophy, colds, neuralgia, rheumatism, and gout. Its antidote is Digitalis.

The alkaloid aconitin is dispensed in the form of pills and tablets, usually of small grainage, $\frac{1}{100}$ down to $\frac{1}{1000}$ or less, and it is also used in ointments. Extracts of both root and leaves occur as such, and in pills alone. Neuralgic pills contain aconite combined with other strong drugs, including morphin, strychnin, arsenous acid, and quinin; one of the old-fashioned so-called "shot-gun" prescriptions contains aconite with Hyoscyamus, ignatia, opium, belladonna, Conium, stramonium, and Cannabis; fever mixtures contain aconite with morphin, tartar emetic, and ipecac; also with Bryonia and belladonna; cold mixtures consist of aconite, quinin, Capsicum, ipecac, and opium; aconite, quinin, ammonium chloride, camphor, opium, and belladonna; aconite, sanguinarin, mor-

phin, atropin, ipecac, tar, and tartar emetic for coughs; aconite, belladonna, aloin, calomel, and quinin; aconite, camphor, opium, and potassium nitrate; aconite, morphin, atropin, and calomel; aconite, Bryonia, belladonna, and mercuric iodide for tonsillitis; aconite, Cimicifuga, belladonna, and Colchicum for sciatica; aconite, quinin, opium, ipecac, and acetphenidin. Aconite is seldom dispensed in liquid preparations owing to the ease with which its active constituent is decomposed. In fact, when the drug is dispensed in pills and tablets it is never safe to depend on its potency unless chemically or physiologically tested, because the manipulation of pill-making is often rigorous enough to break down the highly sensitive aconitin.

The chemical structure of the aconitins is still a subject of research, but it is known that they are all derivatives of bases, probably closely related, known as " aconins."

Dr. Carr [1] in the new edition of Allen has summarized the situation as follows:

Name	Composition	Formula
Aconitin	Acetylbenzoylaconin	$C_{21}H_{27}O_3N$—$(OMe)_4$ (OAc, OBz)
Japaconitin	Acetylbenzoyljapoconin	$C_{21}H_{29}O_3N$—$(OMe)_4$ (OAc, OBz)
Indaconitin	Acetylbenzoylpseudaconin	$C_{21}H_{27}O_2N$—$(OMe)_4$ (OAc, OBz)
Pseudaconitin	Acetylveratrylpseudaconin	$C_{21}H_{27}O_2N$—$(OMe)_4$ (OAc, $OCOC_6H_3(OMe)_2$)
Bikhaconitin	Acetylveratrylbikhaconin	$C_{21}H_{27}ON$—$(OMe)_4$ (OAc, $OCOC_6H_3(OMe)_2$)
Jesaconitin	Benzoylanisylaconin	$C_{21}H_{27}ON$—$(OMe)_4$ ($OCOC_6H_4(OMe)$, OBz)

The bases undergo hydrolysis with ease, yielding the acid components and the parent base. The hydrolysis occurs in stages and in the drug itself there will be found not only the specific aconitin, but its various degradation products. It is due to this latter fact that a chemical assay of an aconite preparation or drug has little value as an indication of the

[1] Commercial Organic Analysis, Allen, Vol. 7, page 257.

therapeutic efficiency. The degradation products are much less active than the alkaloids themselves.

All of the above aconitins are extremely poisonous and if they are suspected, caution should always be observed in testing products physiologically.

Aconitin

This alkaloid is the only crystalline base of A. napellus, but is seldom encountered in a state of chemical purity, being accompanied with the other aconin derivatives of the drug. It may be purified by recrystallizing one of its salts, separating the base, and crystallizing it from alcohol or a mixture of alcohol and ether. It is readily soluble in chloroform and benzol, somewhat less so in alcohol and ether, slightly soluble in hot water, and only sparingly in cold water and petroleum ether. It is dextrorotatory in alcohol and its salts are lævorotatory. The purified base melts 197–198°, but if heated slowly it begins to decompose at 182°, and it will give figures anywhere from this temperature up to 200°. It possesses $(\alpha)_D = +110$ in 3 per cent alcohol.

Aconitin produces a tingling and numbing sensation of the tongue, which spreads to the lips and roof of the mouth and may last for hours. Extremely dilute solutions will produce this sensation and it is one of the best tests, though it must be performed with great caution and only in dilute solutions. To make the test the alkaloid should be dissolved in a little dilute acetic acid and the solution adjusted to 1–1000; then an aliquot of this solution may be diluted to 1–100000 with water and 25 mils taken into the mouth, rinsed well for half a minute between the tongue and cheeks after the manner of a mouth wash and then expelled. If at the expiration of ten to fifteen minutes no tingling sensation has appeared a slightly stronger solution, 1–90000, may be used and so on until the sensation is obtained. If the substance under examination is pure aconitin, the effect will be readily apparent at the dilution of 1–100000, and the author has tested samples which are potent in a dilution of over a million parts of water.

On treating aconitin with nitric acid, evaporating and adding a few drops of alcoholic potash, the characteristic odor of ethyl benzoate is given off. No purple color is obtained on adding the alcoholic potash, but pseudoaconitin is stated to yield a purplish tint.

A solution of great dilution when applied to the eye or upper eyelid causes contraction of the pupil, with a sense of heat and tingling.

Aconitin gives no color reactions on which any reliance can be placed. It is precipitated by the general alkaloidal reagents and some of the insoluble salts form crystals having sharp melting-points and characteristic microscopic forms. The aurochloride is very insoluble and is precipitated

on adding gold chloride to a solution of aconitin in hydrochloric acid in presence of sodium chloride. This salt when washed and dried *in vacuo*, may be obtained in three modifications—from alcohol, aqueous alcohol, chloroform and ether, melting 135°, from absolute alcohol, melting 152°, and on recrystallizing the latter from a mixture of chloroform and ether, melting 176°. The precipitate obtained with potassium permanganate is crystalline and may be obtained from dilutions of 1–500; its crystalline form should be compared under the microscope with the crystals obtained with cocain. Hydrastin and papaverin in concentrated solution are said to give crystalline precipitates with permanganate.

The periodide is very insoluble. Sparingly soluble precipitates are obtained with potassium iodide and ammonium sulphocyanide. Platinic chloride does not give a precipitate unless the solution is very concentrated, mercuric chloride, potassium chromate, ferrocyanide, and ferricyanide give precipitates only in fairly concentrated solutions.

Aconitin is a strong base and forms well-defined salts with mineral acids. It is seldom used in the form of a salt, however, nearly always appearing in medicines as the straight alkaloid. It gives di- and triacetyl derivatives with acetyl chloride, but no derivatives with acetic anhydride.

The hydrolysis of aconitin takes place in two stages, first to acetic acid and benzaconin (picraconitin, napellin, or benzoyl aconin),

$$C_{34}H_{47}NO_{11}+H_2O=C_{32}H_{45}NO_{10}+CH_3COOH,$$

and then benzaconin is further hydrolyzed to benzoic acid and aconin ($C_{32}H_{45}NO_{10}+H_2O=C_{25}H_{41}NO_7+C_6H_5COOH$). The latter is an amorphous, hygroscopic alkaloid, soluble in water, chloroform, alcohol and sparingly in ether. Benzaconin is also present in the aconite root, and is readily soluble in alcohol, ether, and chloroform. It does not produce the characteristic tingling of aconitin and is much less toxic.

Neutral solutions of aconin are lævorotatory, the acid solution is dextro. It reduces Fehling's solution and ammoniacal silver nitrate.

Japaconitin

This alkaloid is obtained from a species of aconite indigenous in Japan, and formerly thought to be A. fisheri, but now considered a distinct species. Japaconitin melts 204–205° and resembles aconitin closely. Its rotation differs somewhat and its hydriodide melts 208–210°, while aconitin hydriodide melts 226°. Its aurochlorides melt 153° (spontaneous evaporation from chloroform) and 231° (separation from alcohol). In its chemical tests it cannot be distinguished from aconitin.

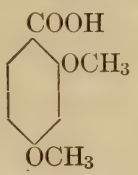
Indaconitin

Indaconitin occurs in A. chasmanthum, a native plant of India. It melts at 202–203° and its rotatory power and that of its salts are somewhat less than those of aconitin. It hydrolyzes in two stages, first to acetic acid and indbenzaconin, and then to benzoic acid and pseudaconin. Its chemical and physical behavior is similar to that of aconitin.

Pseudaconitin

Pseudaconitin differs from the previous bases in containing the veratryl group instead of the benzoyl, and yields veratric acid on hydrolysis with alcoholic potash. Its physiological action is more intense than the other aconite alkaloids. It melts 211–212°. The base is dextro- and its salts lævorotatory. The aurochloride forms yellow needles, melting 236–238°. The nitrate with 3 molecules of water is difficultly soluble and melts 185–186°. It gives a purple-red color when subjected to Vitali's test and a similar color when warmed with concentrated sulphuric acid.

Veratric acid is soluble in alcohol and ether and only slightly soluble in water, and may be removed from an acidulated solution. It crystallizes in prisms containing one molecule of water and melts 178–180°. It is the dimethyl ether of protocatechuic acid.



Pseudaconin, the basic product of hydrolysis, crystallizes from alcohol, melting 94–95°.

Bikhaconitin

This alkaloid like the former contains a veratryl group in its molecule and yields veratric acid on hydrolysis. It crystallizes from ether in white button-shaped masses composed of concentric rings, differing from its related bases in this respect. It melts 118–123°.

Jesaconitin

This is an amorphous alkaloid from A. japonicum and contains no acetyl group. On hydrolysis it yields anisic and benzoic acids and aconin. Anisic acid is paramethoxybenzoic acid, readily soluble in ether, alcohol, and hot water, melting 184° C.

Lycaconitin

Lycaconitin and myoctonin are amorphous bases of A. vulparia. The former is soluble in ordinary organic solvents with the exception of petro-

leum ether, and only sparingly in water. It is precipitated by Mayer's reagent, tannin, bromine water, and iodine, but not by platinic chloride, mercuric chloride, potassium iodide, nor phosphomolybdic acid. Its basic product of hydrolysis is lycaconin, melting 90–92°, soluble in alcohol, chloroform, ether, and benzol and giving a fluorescent solution in water.

Myoctonin

This base is but slightly soluble in ether, but in other respects closely resembles lycaconitin. It yields lycaconin on hydrolysis. It has a bitter taste but does not produce a tingling sensation. It is a strong poison, however, and is reported to resemble curare in its action.

Lapaconitin, Septentrionalin and Cynoctonin

These three alkaloids occur in A. lycoctonum, or according to some authorities in A. septentrionale. Lapaconitin melts 205°, septentrionalin 129°, and cynoctonin 137°. The first mentioned gives fluorescent solutions but the others do not. Lapaconitin is bitter and a heart depressant, the others are local anesthetics.

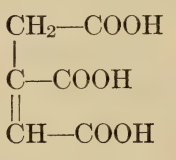
Atisin

This alkaloid occurs in A. heterophyllum and is not toxic. The drug is employed as a bitter tonic. Atisin forms a colorless varnish melting 85°, readily soluble in water and organic solvents except petroleum ether. It is lævorotatory and its salts dextro. With sulphuric acid it gives a yellow color gradually becoming red. It is not hydrolyzed by acids or alkalies but apparently forms a new base.

Palmatisin

Palmatisin occurs in A. palmatum and forms crystals from ether, melting 285°. It resembles atisin in its physiological properties.

Aconitic Acid



Aconitic acid, which appears to be a constant constituent of aconite root, is closely related to citric acid in composition. It forms colorless crystals, melting 186° C. (191° Mullikin), soluble in water, alcohol, and ether. Its aqueous solution gives no precipitate when boiled with excess of calcium hydroxide.

Alkaloid	Formula	Products of Hydrolysis	M. Pt.	$(a)_D$	M. Pt. of Aurichloride	M. Pt. and $(a)_D$ of the first product of hydrolysis	M. Pt. and $(a)_D$ of final product of hydrolysis
Aconitin	$C_{21}H_{27}O_3N$ <(OAc, (OMe)$_4$, OBz)	Acetic acid Benzoic acid Aconin	197–198°	+12.3° in alcohol	135° 152° 176°	Benzaconin amorphous +5.6° in alcohol	Aconin 132° +23° in water
Japaconitin	$C_{21}H_{29}O_3N$ <(OAc, (OMe)$_4$, OBz)	Acetic acid Benzoic acid Japaconin	204°	+23.6° in alcohol	153° 231°	Japbenzaconin 182.3+40.2° in alcholol	Japaconin 97–100° +10.9° in water
Indaconitin	$C_{21}H_{27}O_2N$ <(OAc, (OMe)$_4$, OBz)	Acetic acid Benzoic acid Indaconin	202–203°	+18.2° in alcohol	147° 152°	Indbenzaconin 130–3°+33 6° in alcohol	Indaconin 94–95° +38.2° in water
Pseudoaconitin	$C_{21}H_{27}O_2N$ <(OAc, (OMe)$_4$, OVe)	Acetic acid Veratric acid Pseudaconin	211–212°	+18.6° in alcohol	236°	Veratrylpseudo-aconin 199° = −38.3° in alcohol	Pseudoaconin 94–95°+30.1° in water
Bikhaconitin	$C_{21}H_{27}ON$ <(OAc, (OMe)$_4$, OVe)	Acetic acid Veratric acid Bikhaconin	113–116°	+12.2° in alcohol	232–233°	Veratrylbikh-aconin +29.9° in alcohol	Bikhaconin +33.8° in alcohol
Jesaconitin	$C_{21}H_{27}ON$ <(OAn, (OMe)$_4$, OBz)	Anisic acid Benzoic acid Aconin					
Lycaconitin	$C_{27}H_{34}O_6N_2.2H_2O$	Lycaconin		+31.5° in alcohol			
Myoctonin	?		143–144°	+29.5° in alcohol			
Lapaconitin	$C_{34}H_4O_8N_2$		205°				
Septentrionalin	$C_{31}H_{48}O_9N_2$		129°				
Cynoctonin	$C_{36}H_{54}O_{13}N_2$		137°				
Atisin	$C_{22}H_{31}O_2N$	Atisin monohydrate	85°	−19.6° in alcohol			

The problems which may confront the drug analyst in connection with the aconite alkaloids are as follows: the identification of "aconitin," the determination of the amount present in a mixture, the determination as to whether the amount of alkaloid originally present agrees with that claimed on the label (taking into account the ease with which aconitin decomposes), the question as to the identity of the drug used in compounding an extract of aconite and the actual identity of an aconitin. The word aconitin above is written in quotations in order to emphasize the fact that the identity of an aconitin does not necessarily require one to report the exact individual in question. The first three propositions are those requiring the chief consideration of the analyst, the others may occur in rare cases. Special attention must be called to the third proposition above mentioned; it often happens that a manufacturer acts in perfect good faith and makes up his formula in the proper proportions, but in the course of time, and due to the various hands through which a product must pass to the final consumer and the conditions under which it is kept, its potency becomes impaired and the blame is unjustly carried back to the original source.

In the general scheme of medicinal analysis aconitin will appear when the solution has been made alkaline and shaken out with petroleum ether and with ether. These two fractions will carry a large proportion of the aconitin, the latter the greater proportion unless the quantity is extremely small. The first suggestion of aconitin will occur when a residue evaporated with nitric acid, is treated with alcoholic potash and the characteristic odor of ethyl benzoate is obtained. Cocain will give the same reaction, but if this is followed by a physiological test, conducted by rubbing a minute quantity of the residue on the tongue and lips, cocain produces numbness while aconitin will give the characteristic tingling. Following this a portion of the residue should be dissolved in a small quantity of dilute acid and portions of this solution treated with gold chloride and potassium permanganate, the characteristic forms of the crystals observed under the microscope in comparison with those produced with a known sample of aconitin, and the melting-point of the aurochloride determined. If there is sufficient quantity of the residue and it is not contaminated with other alkaloids it should be crystallized, dried *in vacuo*, and its melting-point determined. When this test is applied the sulphuric acid should be heated to 160–170° before introducing the capillary tube containing the alkaloid, and the acid rapidly heated until the crystals melt.

Unless the analyst is familiar with aconitin he should use great caution in performing the physiological test, and for safety the procedure recommended on page 267 ought to be observed.

In order to determine the amount of aconitin in a fluid, solid extract, or tincture, the procedure recommended in the chapter on Drug Assays

can be used to advantage. The residue will be contaminated to a greater or less extent with other bases, and it may be desirable to dissolve the residue in dilute acetic acid, make up to a definite volume, and then use aliquots of this in a Squibb test, comparing the activity with that obtained with a sample of aconitin of known purity prepared by the worker himself. By this means the quantity of pure aconitin in the original product can be calculated. From mixtures with other non-alkaloid-bearing drugs, aconitin may be separated by extraction from an ammoniacal solution with ether, purified by redissolving in acid, separating any acid or neutral principles by the usual solvents and then removing the aconitin with ether from alkaline solution. The therapeutic activity of a mixture, with respect to the aconitin present, can be obtained by performing a Squibb test on a solution of the original substance precisely as described by Taylor's method on page 27. This procedure is about the only one known for estimating aconitin in mixtures with the other alkaloids with which it is dispensed. No methods have been evolved for separating aconitin chemically from other bases, and any which might be based on its products of hydrolysis are too uncertain to be considered. Of course the base may be easily separated from morphin by shaking it out with ether from a solution made slightly alkaline with caustic alkali. The fact that it is resistant to permanganate, while quinin, strychnin, and many other bases reduce this reagent, is a point which may be used to advantage in solving this problem and offers an attractive field for investigation.

If the amount of aconitin found on analysis does not agree with that claimed, it must not be concluded that the proper quantity was not originally absent. The quantity of acid products of hydrolysis present as well as other basic substances must be determined and the sum total, properly interpreted, used as evidence to substantiate or refute the claim on the label.

The identification of the species of aconitin used in the preparation of a medicine requires careful work. Standard preparations specify the use of A. napellus, and as physicians regulate their dosage on the assumption that the standard drug with which they are familiar, has been employed, and as it appears that the several " aconitins " vary in therapeutic efficiency and possibly physiological activity, any variation in the specific drug employed may lead to disastrous results. Hence the drug analyst may be called upon to settle the question as to whether the drug in hand is A. napellus or some other species. The alkaloid must be separated and carefully purified, and after determining its melting-point and that of its aurochloride, it must be hydrolyzed and both the acid and basic products of hydrolysis identified beyond question. When this is done by referring to the table on page 271 the " aconitin " in hand will be apparent, and when this is determined the drug employed is known.

BASES OF CEVADILLA AND VERATRUM

Cevadilla or Sabadilla seed and Veratrum root possess certain similar physiological properties, especially in relation to their action on the heart, and while there may be no similarity in the chemical composition of the bases, and neither drug possesses an alkaloid in common, unless it be veratridin or cevadin, it is advisable, to avoid confusion, to consider the drugs together. The term " veratrin " has been used for a long time in alkaloidal chemistry and has become so firmly established that, in the minds of many, it is attributed to an individual alkaloid. This is further complicated by the fact that the U. S. and other Pharmacopœias recognize the term, with the amplification that it is " an alkaloid or mixture of alkaloids," and then proceed to describe its properties, even to defining a specific melting-point. As a matter of fact the so-called " veratrin " is really a mixture of the bases obtained from the seeds of Cevadilla, the proportions of which must necessarily vary from time to time. The chief component of " veratrin " is cevadin, an alkaloid which has not been found in the rhizome of Veratrum viride or V. album, and which is apparently different in composition from any of the bases occurring in the latter. Hence we see that the term " veratrin," which will probably always persist, does not apply to alkaloids from the genus Veratrum, and account of this anomaly it is expedient to conjointly discuss the bases of these drugs.

In this introduction attention must be called to an examination of the bases from Zygadenus intermedius conducted by Heyl [1] and his associates, who extracted from the leaves of this plant, called locally Death Camas, a new base to which the name zygadenin has been given and which, in its chemical properties, resembles cevadin. It differs from the latter, however, in its ultimate composition, which is given as $C_{39}H_{63}NO_{10}$, and in having $(\alpha)_D - 48.2°$, while cevadin is inactive.

Prof. Kraemer states that the bulbs of Z. venenosum contain veratralbin, sabadin and sabadinin.

CEVADILLA BASES

Cevadin, $C_{32}H_{49}NO_9$.
Veratridin, $C_{34}H_{53}NO_3$. (?)
Sabadin, $C_{29}H_{51}NO_8$. (?)
Sabadinin, $C_{27}H_{45}NO_8$. (?)
Sabadillin (Cevadillin) $C_{34}H_{53}NO_8$. (?)

The plant Schoenocaulon officinale (Lilaceæ), growing in Mexico and the West Indies, furnishes the seeds from which these bases are obtained,

[1] J. Am. Chem. Soc., 1911, 206; 1913, 258.

and the alkaloidal content varies from 1 to 3 per cent, with cevadin predominating. Tiglic and veratric acid also exist in the drug, either in the free state or in combination. The seeds are not recognized in the U. S. Pharmacopœia, but they find a place in the Swiss standard, and a method of assay is included therewith. American manufacturers apparently make little use of the drug and from all reports the seeds are used chiefly for preparing "veratrin." The ground seed is used as an ingredient for destroying vermin in the hair. The alkaloidal mixture "veratrin" is a drastic and irritant cathartic and has been employed in articular rheumatism, ascites, as a cardiac sedative, and externally in superficial neuralgias, sciatica, and some forms of pruritus. It is a dangerous drug for indiscriminate use and will be rarely found in unknown mixtures.

Cevadin

Cevadin crystallizes from alcohol with 2 molecules of the solvent, which is removed with difficulty when heated to 100° C., but is readily removed with boiling water, and the anhydrous base melts 205–206°. It dissolves in all of the organic solvents except petroleum ether, and its solutions are inactive to polarized light. It is extremely poisonous and has the peculiar property of producing violent sneezing. It gives crystalline salts with gold chloride, picric acid and mercuric chloride, and an amorphous precipitate with platinic chloride. It yields precipitates with the usual alkaloidal precipitants.

The individual color reactions of this base have not been reported. All of the tests described in the literature refer to the mixed bases, and these reactions will be described subsequently.

Cevadin is readily hydrolyzed by aqueous and alcoholic alkaline solutions. It is first transformed to angelic acid and a new base called cevin. Then angelic acid changes to the isomeric cevadic or tiglic acid, which is partly broken up into acetic and propionic acids, and the cevin forms non-basic resinous products. The products of hydrolysis may be obtained by boiling the base with alcoholic potash under a reflux condenser, diluting, acidifying, and shaking out the acid products with ether, and then making alkaline and removing cevin by amyl alcohol. The ether solution of the acids is evaporated and the residue distilled, and as the fraction coming over at 180–190° is collected and cooled, it will yield crystals of tiglic acid, melting 64–65°. Tiglic acid is methyl crotonic acid,

$$CH_3CH{=}C(CH_3)COOH.$$

Cevin obtained on evaporating the amyl alcohol, melts 145° and dissolves in alcohol and acids, but only sparingly in chloroform, and scarcely

in ether. It is precipitated by caustic alkalies, but not by carbonates, and reduces Fehling's solution and ammoniacal silver nitrate.

Veratridin

This is an amorphous base, and its properties are not well known owing to the difficulty of obtaining it pure. It melts at 150° or 180° and forms a fairly insoluble nitrate and sulphate. On hydrolysis it yields veratric or dimethyl protocatechuic acid and a basic product, verin or veratroidin, which bears a close resemblance to cevin obtained from cevadin. Veratric acid is one of the products of hydrolysis of pseudaconitin and has already beeen described.

Sabadin

Sabadin is a crystalline base, melting 238–240°. It is precipitated from its solutions by warming with sodium carbonate, and shaking with ether. On subsequent crystallization from alcohol it is only sparingly dissolved in ether. It is claimed to give no color with nitric acid, but dissolves in sulphuric acid with a yellow color and green fluorescence, which soon disappears, and a blood-red to violet shade develops.

Sabadinin

This base is separated in a similar manner to sabadin which it resembles in some of its properties and color tests thus far studied. It melts 160° and does not produce sneezing.

Sabadillin

Sabadillin has been reported as occurring in commercial veratrin. It yields tiglic acid on hydrolysis.

The above descriptions of the bases show that, with the possible exception of cevadin, the chemistry of this group is still in its pioneer state. From an analytical standpoint we can only consider the alkaloids *en masse*, because as yet we know little or nothing of the solubilities of the subsidiary bases, and there is no scheme for separating them when they occur in the quantity usually available.

There are several color tests attributed to the purified residue. Sulphuric acid dissolves the bases to a yellow solution with a greenish fluorescence, changing to blood-red and finally to purple. Hydrochloric acid gives a permanent blood-red, and nitric acid a yellow solution, often pinkish at moment of solution. Sulphuric acid containing furfurol gives a dark-green color becoming violet on warming.

These tests, taken in conjunction with the physiological action of the alkaloids (intense sneezing), and the production of the characteristic acids on hydrolysis, furnish the necessary evidence for deciding as to the identity of the bases and the drug from which they are obtained. None of the cevadilla bases give reactions which might confuse them with the opium, Nux Vomica, coca, belladonna, and cinchona bases, for all of which there are certain well-defined tests.

There is, however, some likelihood of mistaking a mixed residue from Veratrum viride or V. album for one from Cevadilla, as the former contains veratralbin, which resembles cevadin in its properties and gives rise to a series of color reactions similar to those above described.

With the exception of veratralbin, most of the Veratrum bases when isolated are but sparingly soluble in ether. However, this property cannot be depended upon for making a separation from alkaline solutions with immiscible solvents, as jervin and probably the other bases are fairly soluble in ether when freshly precipitated. Protoveratrin and protoveratridin are but sparingly soluble in ether or chloroform, and portions may still be found in the alkaline solution after shaking out with these solvents. The solubility of the cevadilla bases is such that they are practically all removed by ether from alkaline solution.

THE VERATRUM ALKALOIDS

Jervin, $C_{26}H_{37}NO_3$.
Rubijervin, $C_{26}H_{43}NO_2$.
Pseudojervin, $C_{29}H_{43}NO_7$.
Protoveratrin, $C_{32}H_{51}NO_{11}$.
Protoveratridin, $C_{26}H_{45}NO_8$.
Veratralbin, $C_{28}H_{43}NO_5$ or $C_{32}H_{53}NO_9$.

The roots of Veratrum album from Southern Europe and of V. viride, Bunch flower family (Melanthiaceæ), from the United States and probably other related species contain these alkaloids. Wright reports cevadin in the roots of V. viride and possibly veratridin. The two species mentioned are official in the U. S. Pharmacopœia. V. viride, called the American hellebore, is a native perennial herb, 2 to 7 feet high growing in swamps, wet woods and meadows, closely associated with skunk cabbage. It produces large bright-green leaves and is a very conspicuous plant in the meadows and swamps.

Veratrum is employed medicinally in the form of its extract, but its use is limited and is attended with so much danger that it will seldom be encountered in practice. It is present in small dosage in liver pills mixed with jalap, aloes, gamboge, leptandra, Podophyllum resin, Capsicum,

croton oil, and calomel. It is a heart depressant and is used in certain aortic conditions.

The percentage of total bases in V. viride seems to vary considerably running from .2 to over 1 per cent. In V. album, Wright found over 4 per cent of alkaloids with veratralbin predominating, though he reported but a trace in V. viride, cevadin, and jervin being the chief bases in the latter.

Jervin

Jervin crystallizes in white acicular prisms containing $2H_2O$, and on drying at 100° it melts 241°. It is readily soluble in chloroform, less so in alcohol and ether, and almost insoluble in benzol and petroleum ether. It is not hydrolyzed by boiling alcoholic potash. It is a strong base and forms well-defined salts, the acetate and phosphate being easily dissolved in water, but the hydrochloride, nitrate, and sulphate are only sparingly soluble especially in the presence of the free acid. The less soluble salts may be prepared by treating a solution of the phosphate or acetate with the alkali salt of the acid.

Jervin gives a yellow color with sulphuric acid, changing to brownish, greenish brown, and on longer standing to green, which finally disappears. Pseudojervin also gives the green shade, but the other Veratrum bases ultimately produce a reddish tint. Sulphuric acid and sugar produce a violet color, changing to blue. This reaction is not very satisfactory, however, as the mixture first becomes dark brown and after a time a violet tint appears along the edges and in thin layers, and then gradually turns blue. Froehde's reagent acts in the same manner as sulphuric acid alone. Nitric acid gives a pinkish tint, the solution soon turning orange and then slowly fades. Hydrochloric acid gives a light yellow color.

Precipitates are obtained with the common alkaloidal reagents including tannic acid.

Rubijervin

Rubijervin crystallizes in acicular prisms containing one molecule of water, and on drying melts 234°. It is somewhat soluble in alcohol, hot chloroform, and benzol, and slightly soluble in ether and petroleum ether. Its salts are much more soluble than those of jervin. It gives a yellow solution with sulphuric acid, turning brownish, reddish brown, and finally purplish. If the brownish-red liquid is diluted with water, the color changes to crimson and passes through several violet and purple shades to deep blue. It is precipitated by the common alkaloidal precipitants with the exception of tannic acid and platinic chloride.

Pseudojervin

Pseudojervin crystallizes in hexagonal plates, melting 304°. It is readily soluble in chloroform, slightly soluble in alcohol and benzol, and practically insoluble in ether and petroleum ether. The sulphate is slightly soluble in cold but readily in hot water, and the hydrochloride is only sparingly soluble in water either hot or cold, but is dissolved in water containing a little free acid.

With sulphuric acid it gives the same color tests as jervin, and is precipitated by the same reagents except platinic chloride.

Veratralbin

This alkaloid is amorphous and melts at 149°. Its salts are amorphous. It dissolves easily in the ordinary organic solvents. Its color reactions are similar to those obtained with cevadin; sulphuric acid produces a yellow color, changing to orange and blood-red with a greenish fluorescence; nitric acid a fleeting rose tint, the solution becoming pale yellow; dilute hydrochloric acid a rose color. It is precipitated by the common alkaloidal reagents.

Protoveratrin

This alkaloid, which seems to be the most active of the group, crystallizes in microscopic plates, melting 245–250°. It is sparingly soluble in the organic solvents. It gives a green color with sulphuric acid which passes through blue to violet. Hydrochloric and phosphoric acids give a dark cherry red and a butyric odor. It is not precipitated by tannic acid, platinic chloride, or mercuric chloride, but is thrown down by the other common reagents.

It is stated that protoveratrin may be separated from the other bases by treating an acetic acid solution with solid glacial phosphoric acid, filtering, and extracting the protoveratrin with ether after rendering ammoniacal.

Protoveratridin

This base crystallizes in plates melting at 265°. It is insoluble in ether, benzol, and petroleum ether and only to a slight extent in alcohol and chloroform. With sulphuric acid it gives a violet to cherry-red color and with hydrochloric acid a bright red color and a butyric odor. It is not precipitated by platinic chloride or potassium cadmium iodide.

An alkaloidal residue consisting of the Veratrum bases will give indications of its identity by evolving a butyric odor when treated with acids at the same time its color reactions are determined. The mixed bases

will give negative tests with the reagents employed for the other well-known alkaloids.

Farr and Wright have evolved a method for separating jervin from its accompanying bases. The alkaloidal residue is dissolved in 2 per cent acetic acid, filtered, a few crystals of potassium nitrate added, shaken until dissolved and the solution allowed to stand. The crystals of jervin nitrate which deposit on standing are filtered, washed with a little water and then treated with chloroform and a little dilute ammonia. The jervin dissolves in the solvent and may be obtained by evaporating. If the analyst can obtain sufficient material, this test will furnish the best evidence of the presence of Veratrum in a medicinal preparation.

CHAPTER IX

ALKALOIDS WITH NO PYRIDIN NUCLEUS AND THOSE OF UNKNOWN COMPOSITION

COLCHICIN, $C_{15}H_9(NHCOCH_3)(OCH_3)_3(COOCH_3)$

THE meadow saffron, Colchicum autumnale L. (Liliaceæ), contains the alkaloid colchicin and probably some of its degradation products. The parts of the plant used commercially are the bulbous root, called the corm, and the seed. The alkaloid is present in amounts varying from 0.2—0.5 per cent.

Colchicum extract and the alkaloid colchicin have long been used for relieving gout and rheumatism, and should always be looked for in preparations recommended for these ailments. Wine of colchicum is extensively employed in some localities, and one of the most widely advertised proprietaries is a globule containing colchicin dissolved in methyl salicylate. Colchicum extract is combined with Hyoscyamus, colocynth, and calomel, and also with aconite. Colchicin is often combined with salicylates in liquid form, also with potassium iodide, digitalin, Phytolacca, codein, quinin, and opium.

Colchicin is the methyl ester of colchicein or acetotrimethylcolchicinic acid, and on heating with mineral acids it is readily split up into methyl alcohol and colchicein. The latter, on heating with hydrochloric acid, loses an acetyl group as acetic acid, and then three methyl groups as methyl chloride, leaving colchicinic acid, $C_{15}H_{11}N(OH)_3(COOH)$. Colchicein has the composition $C_{15}H_9(NHCOCH_3)(OCH_3)_3(COOH)$.

Colchicin is a weak base and one of the few yellow alkaloids, resembling berberin in this respect, but differing from it in being completely removed from its solutions even when acid, by chloroform. As usually obtained it is a resinous mass which melts with decomposition at about 140–145°. In its crystalline form it melts 120°. It is readily soluble in alcohol and water, and quite readily in chloroform and benzol, but is difficultly soluble in ether and practically insoluble in petroleum ether. Its aqueous solution is lævorotatory. Its solution in dilute acids gives precipitates with most of the alkaloidal reagents except platinic chloride. In aqueous solution chlorine and bromin water give yellow precipitates which dissolve in ammonia with an orange color.

Colchicin dissolves in concentrated sulphuric acid to a yellow solution, and on adding a drop of nitric, the color changes to green, blue, violet, wine red, and finally green; addition of concentrated sodium hydroxide in slight excess then gives an orange red. It dissolves in nitric acid with a deep purple or bluish color. It gives a yellowish-green solution with ammonium vanadate; a green color soon fading with sulphuric acid and bichromate; and with formaldehyde sulphuric acid the crystals become reddish and the liquid yellow. An aqueous solution of colchicin heated on the steam-bath for one-half hour with 5 drops of 20 per cent hydrochloric acid and subsequently treated with 3 to 5 drops of ferric chloride solution will develop a green color, and on cooling and shaking out with chloroform the latter will separate either yellowish or permanganate red, depending on the amount of colchicin present. If the colored liquids are too opaque, the mixture must be diluted with water. The red tint will not appear unless the amount of colchicin be over 2 milligrams.

It combines with chloroform to form opaque needles with a mother-of-pearl luster. This substance loses chloroform when heated to 100° C. or when warmed with water. It is now being marketed as a medicinal product. Colchicin also forms a crystalline compound with ether.

A non-poisonous substance giving many of the reactions for colchicin has been found among the normal constituents of beer, being apparently derived from hops. Putrefying cadavers yield substances which bear a close resemblance to colchicin, and might easily be mistaken for this alkaloid in toxicological work.

Colchicein, its first degradation product, forms shining needles with $\frac{1}{2}H_2O$. The water may be driven off at 140–150° and the anhydrous substance then melts 160–170°. It is slightly soluble in cold water, readily soluble in alcohol and chloroform, and almost insoluble in ether and benzol. On account of the ease with which colchicin is hydrolyzed, it is probable that colchicein is present to a greater or less extent in most of the colchicin residues obtained in analytical work. It is soluble in alkalies and alkali carbonates, and with acids forms yellow solutions.

Colchicin may be readily detected in the mixtures in which it is commonly employed on account of its solubility in chloroform from a neutral or acid solution. It will seldom if ever be found combined with berberin, and if the latter is present, the greater part will remain in solution until the final shake-out with alcohol—chloroform according to the regular scheme. When colchicin occurs combined with Hyoscyamus, aconite, opium, codein, or quinin it will be completely separated from all of the other alkaloids except possibly narcotin, narcein, and papaverin, when the acid solution of the crude alkaloids is shaken out with chloroform. The presence of the above mentioned opium alkaloids in the residue will be at once apparent on adding formaldehyde-sulphuric acid. When col-

chicin occurs mixed with salicylates, the salicylic acid will of course appear in the chloroform residue from an acid shake out; if the residue is then dissolved in chloroform and the solution shaken out with sodium hydroxide, the salicylic acid will be completely removed. In some cases before subjecting a colchicin residue to the color tests and other reactions for its identification, it will be advantageous to purify the alkaloid by precipitating, as the iodine compound as described under the assay of colchicum.

The preliminary treatment of the samples in which it is desired to find colchicin, should follow the usual lines customarily employed when working with organic mixtures. An exception should be made, however, in the case of the globules of colchicin and methyl salicylate. The medicament should be washed out with petroleum ether, poured into a separatory funnel, and then shaken out with dilute hydrochloride acid to remove the colchicin. The alkaloid can be recovered from the acid by agitation with chloroform.

Quantitative Methods.—The separation and determination of colchicin in wine of Colchicum and in Colchicum preparations generally may be carried out according to the procedure described under the assay of colchicum. If the sample is a liquid, 25–50 mils should be taken as a sample, the bulk of the alcohol evaporated on the water-bath and the residual solution transferred to a separator with water and petroleum ether, then made slightly acid with hydrochloric acid and the colchicin extracted with chloroform and purified. After removing the crude colchicin the acid aqueous liquid can be set aside and later treated with excess of ammonia and any atropin, aconitin, codein, quinin, or morphin determined by shaking out with the proper solvents.

If salicylates are present the procedure must be modified by dissolving the crude colchicin in chloroform, transferring to a separator and shaking out two or three times with dilute sodium hydroxide to remove the salicylic acid. The alkaline liquid is then washed once with fresh chloroform, the latter added to the chloroform containing the colchicin, the whole filtered and evaporated.

If the sample is a pill or tablet 10–20 units should be ground in a mortar and extracted four to five times with alcohol, the alcoholic solution filtered, 20 mils water added and after evaporating most of the alcohol, the assay continued as described above.

ASSAY OF GLOBULES OF COLCHICIN AND METHYL SALICYLATE

For assaying globules of colchicin and methyl salicylate, a dozen or more of the globules should be pierced and the contents poured into a weighing tube. A weighed quantity of the liquid is then transferred to a separator with petroleum ether, and the mixture shaken out with dilute

hydrochloric acid until the colchicin is entirely removed, four extractions in general being sufficient. The colchicin may then be recovered from the acid by shaking out with chloroform. It it is desired to determine the amount of methyl salicylate in the petroleum ether solution, after the acid treatment, it is transferred to a flask of about 200 mils capacity, 50–100 mils of alcoholic potash added, and the contents boiled under a reflux condenser until the methyl salicylate is entirely saponified. The alcohol is then evaporated, the solution poured into a separator, the salicylic acid set free by mineral acid and shaken out with ether from which solution it may be determined by titration with standard alkali, or by removing with sodium bicarbonate and precipitating with iodine, the details of which are described under salicylic acid, page 676. The factor for methyl salicylate is 1.1014.

THE XANTHIN BASES

Xanthin, $C_5H_4N_4O_2$.
Caffein, $C_8H_{10}N_4O_2$.
Theobromin, $C_7H_8N_4O_2$.
Theophyllin, $C_7H_8N_4O_2$.
Hypoxanthin, $C_5H_4N_4O$.
Guanin, $C_5H_5N_5O$.
Adenin, $C_5H_5N_5$.

These bases occur naturally in some or all of the following: tea, coffee, cocoa, Paraguay tea or maté, guarana, and cola.

Tea leaves contain all except theobromin and guanin, the caffein comprising from 2 to $2\frac{1}{2}$ per cent.

Cocoa beans (Cacao seed) contain from 1 to 4 per cent of theobromin and a small amount of caffein.

Coffee leaves contain 1 to 3 per cent of caffein alone, and the beans from .5 to 2.5 per cent caffein alone.

Paraguay tea contains from 1 to 2 per cent of caffein alone.

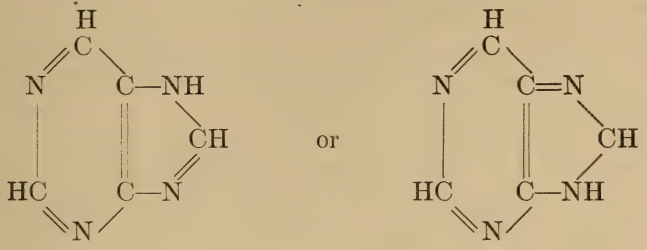
Guarana contains as high as 5 per cent of caffein alone.

Cola contains from 2 to 3 per cent of caffein and a little theobromin, about .02 per cent.

The last four bases are found in the seeds, buds and roots of a large number of plants, and also occur widely distributed in the animal kingdom, having been observed in almost all the organisms of the higher animals and are probably decomposition products of nuclein. They are derivatives of purin, $C_5H_4N_4$. Their constitutional characteristics have been developed by Fischer.

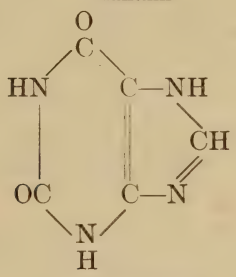
Purin is also the mother substance of uric acid. This latter is a trioxypurin and from it purin may be prepared.

The constitution of purin is seen by the following structural formulæ: Derivatives of both forms are known.



The most important member of this group is caffein, and it will be found very extensively in medicinal preparations. Theobromin present in cocoa will also be met with to some extent, but the other bases will seldom be found except in meat products and preparations of this type.

Xanthin



2–6 dioxypurin

Xanthin occurs naturally in tea leaves, the juice of the beet, shoots of lupine and barley, and is not liable to be met with to any extent in drug analysis. It is usually present in meat products and it is in preparations of this type that it might be found.

It separates from its aqueous solution as a white powder, and when heated it decomposes above 150° without melting, and evolves carbon dioxide, ammonia, and hydrocyanic acid. It is almost insoluble in cold water, and very little soluble in hot water; insoluble in alcohol and ether. It is a weak, monoacid base, has acid properties and unites with bases to form salts containing two equivalents of the metal. These salts are very unstable, being decomposed by carbon dioxide and water. Xanthin is soluble in caustic alkalies, but is precipitated by adding an acid or even passing carbon dioxide gas through the mixture. It is dissolved by warm ammonia, which distinguishes it from uric acid. Mercuric chloride precipitates xanthin in very dilute solutions. Cupric acetate produces no precipitate in the cold, but on heating a flocculent apple-green precipitate

is produced. An ammoniacal solution of xanthin gives precipitates with zinc chloride, calcium chloride, and lead acetate.

On treatment with potassium chlorate and concentrated hydrochloric acid it is oxidized to urea and alloxan, and on evaporating the solution to dryness and exposing to the fumes of ammonia a bright pink color develops. This is known as the murexide reaction.

Xanthin dissolves in hot nitric acid without evolution of gas. On careful evaporation of the solution a yellow residue remains, which turns reddish yellow on addition of caustic potash or soda, and on subsequent heating becomes reddish violet. If ammonia be substituted for the fixed alkali, no violet coloration is obtained. This test distinguishes xanthin from uric acid, which gives the characteristic murexide reaction when similarly treated.

If solid xanthin be sprinkled on a solution of caustic soda mixed with bleaching powder, each particle becomes surrounded with a dark ring or scum, which rapidly becomes brown and then disappears.

Xanthin may be converted to theobromin by treating its lead salt with methyl iodide and heating to 100°.

$$C_5H_2N_4O_2Pb + 2CH_3I = C_5H_2N_4O_2(CH_3)_2 + PbI_2$$

It may be converted to caffein by heating it in aqueous alkali with methyl iodide.

$$C_5H_4N_4O_2 + 3CH_3I + 3KOH = C_5HN_4O_2(CH_3)_3 + 3KI + 3H_2O$$

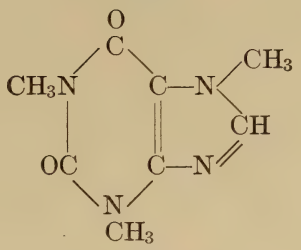
In the general run of drug assaying it is doubtful if one would be called upon to make a quantitative estimation of xanthin bases other than caffein and theobromin, but in case it becomes necessary to determine these bodies, attention is directed to the following method:

Xanthin Bases. (Schittenhelm's Method.)[1]—Dissolve from 3 to 5 grams of the extract in 100 mils of water, transfer to a large evaporating dish, and add 500 mils of a 1 per cent solution of sulphuric acid. Heat on the water-bath for four or five hours, finally evaporating to a volume of from 75 to 100 mils, neutralize with potassium hydroxide, using litmus paper as an indicator. Transfer to a beaker, add 15 mils of a 15 per cent solution of sodium bisulphate and from 15 to 20 mils of a 15 per cent solution of copper sulphate, cover with a watch-glass, and let stand overnight. Filter and wash with dilute copper sulphate. Return the precipitate to the original beaker, add sodium sulphide, acidify with acetic acid and warm on the steam-bath. Filter hot and wash with hot water. Treat the filtrate with 10 mils of 10 per cent hydrochloric acid and evaporate it on the steam-bath to about 10 mils. Filter and wash, make ammoniacal

[1] Bull. 90, U. S. Dept. of Agriculture, page 129.

and add in slight excess a 3 per cent solution of ammoniacal silver nitrate. Let stand overnight, filter, wash out all ammonia carefully, and determine nitrogen in the precipitate. The result is the nitrogen of the xanthin bases.

Caffein



1–3–8 Tri Methyl Xanthin or
1–3–8 Tri Methyl—2–6 Dioxypurin

Caffein was discovered in the coffee berry in 1820, and it occurs in this plant in combination with citric and tannic acids. It occurs also in tea, guarana, Paraguay tea, cola nut, and the seeds of cacao. The base is present in the plants in the free state to some extent, but it also occurs combined with acids and probably also in the form of glucosides. This renders a simple, complete extraction of caffein from drug extracts difficult if not impossible, and it becomes necessary to treat the products with acids or alkalies in order to effect hydrolysis or separation from the plant acids.

In medicinal preparations, particularly of the headache mixture type, caffein will be found in the alkaloidal form. Guarana extract will be met with both in the liquid and solid form. Cola preparations are found quite extensively on the market, but extracts of coffee or tea will be met with only sparingly. Caffein and preparations of guarana and cola occur in products which are designed to cause stimulation and in tonics for the nervous system. Headache mixtures nearly always contain caffein, and it will be found in diuretic compounds and in some heart tonics. It is used to a large extent as an ingredient of popular beverages.

Caffein and caffein-containing drugs will be found in products of the following types:

Elixir celery compound, containing celery seed, coca, kola, and often Viburnum prunifolium; elixir kola compound, containing celery seed, kola, and coca; kola wine and kola cordial; elixir celery and guarana; elixir acetanilid compound, containing acetanilid, caffein, sodium bromide, codein, and Gelsemium; elixir migraine, containing acetanilid, caffein, and sodium bromide; liquid headache mixtures contain caffein together with acetanilid, acetphenetidin, antipyrin, bromides, and often aromatic spirit of ammonia; pills are marketed containing extract of kola and

extract of guarana, but most of the caffein bearing-preparations of this kind contain the alkaloid caffein; cardiac pills containing caffein, Digitalis, glonoin and Strophanthus, and sometimes codein; compressed tablets for relieving headache contain caffein and acetanilid, and often acetphenetidin or antipyrin, or some combination of these substances with bromides and sodium bicarbonate; migrain tablets contain caffein and camphor monobromate; neuralgic tablets contain caffein with Hyoscyamus and morphin.

Caffein is a feeble base, but forms definite compounds with mineral acids, which, however, are easily broken up in aqueous solutions. It crystallizes in fleecy masses of long, flexible, white crystals, having a silky luster, odorless, with a bitter taste, and permanent in the air. Its reaction is neutral to litmus.

It is soluble at 15° C. in 80 parts of water, 33 parts of alcohol, seven parts of chloroform, and about 550 parts of ether. It is readily soluble in boiling water, chloroform, alcohol, amyl alcohol, and benzol, less soluble in ether, and only slightly in carbon bisulphide and petroleum ether.

It does not evaporate with the vapor of water, and undergoes no appreciable change at 100° C. except that its water of crystallization, 1 molecule, is expelled. At 100° it volatilizes very gradually, and at a high temperature it sublimes unchanged. At 229° C. it melts to a colorless liquid. It readily undergoes decomposition when boiled with limewater, but decomposition is insignificant when boiled with magnesium oxide and water, and no change occurs with lead oxide.

It may be oxidized by nitric acid or by hydrochloric acid and potassium chlorate, the products of oxidation including amalic acid, which on subsequent treatment with ammonia goes over to murexoin, which has a brilliant purplish-pink color. Uric acid and oxidizing agents give alloxanthin, $C_8H_6N_4O_8$, and with ammonia this latter is converted into murexide, $NH_4C_8H_4N_5O_6$. Theobromin and xanthin give a reaction similar to caffein. The purple coloration in case of caffein and theobromin is decolorized by caustic alkali, but that due to uric acid is changed to blue.

An aqueous solution of caffein is not precipitated by potassium-mercuric iodide test solution. This is also true of theobromin. A neutral aqueous solution is not precipitated by a solution of iodin and potassium iodide, but in an acid solution, caffein is precipitated quantitatively. Its solution in water (1 to 200) gives an abundant precipitate on adding a saturated solution of mercuric chloride. More dilute solutions give less immediate precipitate. Tannic acid gives a precipitate soluble in excess of the reagent. Potassium-bismuth iodide precipitates caffein from moderately dilute solutions after a time. Phosphomolybdic acid gives a yellow precipitate, soluble in warm sodium acetate solution, and depositing free caffein on cooling. Platinic chloride and hydrochloric acid added to a

concentrated solution gives an orange-red precipitate, soluble in 20 parts of cold and smaller amounts of warm water, crystallizing again on cooling.

The solubility of caffein in water is increased by the presence of certain substances, such as sodium bromide, sodium benzoate, sodium cinnamate, sodium salicylate, and antipyrin.

Caffein may be completely removed from an acid aqueous solution by shaking out with chloroform.

Caffein is removed from an aqueous solution by charcoal, but when dissolved in chloroform the solution may be shaken with charcoal without any absorption of the base. Lead sulphide will carry down caffein when precipitated from solutions clarified by lead acetate.

Caffein may be separated from theobromin by treating the mixed alkaloids with cold benzol, in which theobromin is practically insoluble.

QUANTITATIVE DETERMINATION OF CAFFEIN

The methods for the determination of caffein in fluid extracts of guarana and kola have already been described.

In all cases where caffein is present wholly or partly in the form of a drug extract caution must be observed that the caffein compounds are thoroughly broken up so that the alkaloid will be completely extracted.

Many methods for the estimation of caffein in tea or coffee have been published and most of them are unsatisfactory and unreliable. The Association of Official Agricultural Chemists require the use of the modified Stahlschmidt method in official work for determining the caffein in tea, and the Gorter method for coffee.

Modified Stahlschmidt Method.—Weigh 3.125 grams of the finely powdered sample into a 500-mil flask, add 225 mils of water (this volume will shrink to about 200 mils by boiling), attach a reflux condenser and boil for two hours. Add 2 grams of dry basic lead acetate and boil ten minutes more. Cool, transfer to a 250-mil graduated flask, fill to the mark, filter through a dry filter, measure 200 mils of the filtrate into a 250-mil graduated flask and pass hydrogen sulphide through it to remove the excess of lead. Make the solution up to the mark and filter through a dry filter. Measure 200 mils of this filtrate into an evaporating dish and concentrate to about 40 mils. Wash the concentrated solution with as little water as possible into a small separatory funnel and shake out four times with chloroform, using 25, 20, 15, and 10 mils, respectively. If any emulsion forms, break it up with a stirring rod and run the separated portions of chloroform through a 5-c.m. filter paper into a small, tared Erlenmeyer flask. Evaporate off the chloroform on the steam-bath, or recover the chloroform by attaching the flask to a condenser and distilling to a small volume. Dry the fine, white crystals of caffein to con-

stant weight at 75° C. Test the purity of this residue by determining nitrogen and multiplying by the factor 3.464.

Gorter Method.—Moisten 11 grams of finely powdered coffee with 3 mils of water, allow to stand thirty minutes and extract with chloroform for three hours in a Soxhlet extractor. Evaporate the extract, treat the residue of fat and caffein with hot water, filter through a cotton plug and moistened filter paper and wash with hot water. Make up the filtrate and washings to 55 mils, pipette off 50 mils and extract four times with chloroform. Evaporate the chloroform extract in a tared flask, dry the caffein at 100° C., and weigh. Transfer the residue to a Kjeldahl flask with a small amount of hot water and determine nitrogen. To obtain the weight of caffein multiply the result by 3.464.

From most of the alkaloids with which it may occur combined, caffein may be separated by taking advantage of the fact that it can be removed from acid solution by chloroform, the other bases being retained. This, however, is not the case when acetanilid, acetphenetidin, and antipyrin are present, and special methods of separation have been provided which will be found on pages 795, 837 and 857.

In the case of liquid preparations containing caffein in the form of base, or when present in the form of kola, guarana, coffee or tea; or combined with alkaloids such as cocain, morphin, strychnin, and atropin; weigh or measure accurately the sample, transfer to a medium sized evaporating dish, add ammonia and digest for four hours and evaporate over steam-bath until no further diminution in volume takes place. Treat the residue with alcohol, warm, then cool and decant washings into another evaporating dish. Repeat the process four or five times if necessary should the residue contain much gummy material. Add water to the alcoholic solution, and then evaporate over steam-bath until all alcohol is driven off. Transfer to a separatory funnel, washing out dish with water and render the solution slightly ammoniacal. Shake out with four successive portions of chloroform using 15 to 20 mils each time. The chloroform now contains all the caffein and if any other base is present this is also dissolved, morphin of course to a very limited extent. Now shake out with three successive portions of 2 per cent sulphuric acid, which will remove all the bases except caffein and preserve the acid solution.

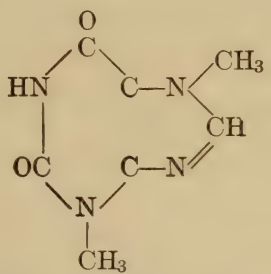
Filter the chloroform solution into a tared dish, washing the funnel, filter paper, inside of funnel, and stem of funnel with chloroform and evaporate to dryness at 100°. If the residue of caffein is colored, or contains grease or has much odor it should be dissolved in dilute hydrochloric acid, transferred to a flask, and an excess of strong solution of iodine in potassium iodide added. Rotate the flask until the caffein iodin compound agglomerates and let stand overnight. Filter, wash precipitate once with iodin solution, discarding washing and not attempting to remove the last por-

tion of precipitate from flask in which precipitation was made. Pour a solution of sulphurous acid over filter or place a crystal of sodium sulphite on the filter, add water and 1 to 2 mils of hydrochloric acid and run the liquid into the flask in which the original precipitation was made; wash filter paper with sufficient of the liquid to decompose the iodine compound and then place filter paper in flask and heat for ten to fifteen minutes over the steam-bath. Cool, filter into separatory funnel, wash out flask three times with water. Render ammoniacal and shake out three times with 15- to 20-mil portions of chloroform. Run chloroform through filter into a tared dish, using precautions of washing with chloroform as above mentioned. Evaporate to constant weight at 100°.

In some instances a dye stuff will stay with the caffein, but this may be removed by shaking the chloroform solution with a strong solution of sodium bisulphite.

The other alkaloids having been separated by the above mentioned method by shaking out with acid can now be determined. The details and precaution to be observed are described under the particular alkaloid in question.

Theobromin



3–7 dimethyl 2–6 dioxypurin or 3–7 dimethylxanthin.

Theobromin occurs in cacao beans combined with malic acid. It also occurs in small amounts in kola nuts.

Theobromin is a diuretic and a nerve stimulant and its compounds with benzoates, salicylates, etc., have a limited use in medicine. Urocitral is a mixture of molecular amounts of theobromin and sodium citrate; agurin of theobromin and sodium acetate; uropherin B of theobromin and lithium benzoate; uropherin S of theobromin and lithium salicylate. Iodotheobromin consists of 40 per cent theobromin, 21.6 per cent sodium iodide and 38.4 per cent sodium salicylate.

Chocolate is used in some preparations in order to make them palatable and the analyst will probably find theobromin here. Its presence or absence will also be valuable evidence in determining whether many of the so-called " chocolate-coated tablets " are actually covered with chocolate or only iron oxide encased in sugar.

Theobromin crystallizes in the anhydrous state and forms microscopic needles, melting 329–330° C. in a closed tube. When heated exposed to the air it sublimes without melting at 290–295° C.

It is soluble in amyl alcohol, fairly soluble in chloroform, alcohol and water when hot, slightly soluble in benzol, ether, cold water, and alcohol, and insoluble in petroleum ether and carbon tetrachloride. It is soluble in acids and precipitated by alkalies, but soluble in excess of caustic alkali or ammonia. It is wholly extracted by chloroform from its solutions in caustic alkalies.

It is a weak monoacid base, neutral, and its salts are decomposed by water. It does not combine with alkyl iodides. It possesses acid properties and forms definite salts, the sodium and barium salts having been studied.

Theobromin gives a white crystalline precipitate with mercuric chloride, sparingly soluble in water and alcohol.

It forms with silver nitrate a definite and insoluble compound, $C_7H_8N_4O_2AgNO_3$, which is only sparingly soluble in water and may be dried unchanged at 100° C.

With solution of sodium phosphotungstate it gives in acid solution a yellow precipitate. This may be mixed with sodium carbonate or magnesium oxide, dried, exhausted with chloroform and the theobromin recovered.

When boiled with concentrated barium hydrate solution or alkalies it yields no product similar to caffeidin.

Theobromin gives with oxidizing agents and ammonia the same color reactions as caffein.

If 0.05 gram theobromin is treated with 3 mils water and 6 mils sodium hydroxide solution, and to the mixture 1 mil ammonia and 1 mil 10 per cent silver nitrate added, solidification takes place on shaking, the mass will liquefy at 60° C., and on cooling a transparent jelly results which will withstand the action of light for a week or more. Caffein does not give this test, and theobromin may be separated from caffein by precipitating it as the silver nitrate compound.

Estimation of Theobromin

Method of Decker as Modified by Welman.—Boil 5 grams of powdered cacao seeds which have not been freed from fat, or 10 grams of chocolate, for an hour in a large Erlenmeyer flask under a reflux condenser with 5 grams of magnesium oxide (calcined magnesia) and 300 mils of water. Let the flask stand upon a boiling water-bath until the suspended matter has settled and then pour the hot, supernatant liquid through an asbestos filter. Wash the residue in the flask twice with

200-mil portions of boiling water. Pour the clear liquid through the same asbestos filter. It is advisable to use a water pump in filtering. Boil the residue again for an hour under a reflux condenser with 2 grams of magnesium oxide and 300 mils of water, decant, and filter. Mix all the filtrates with ignited sea sand and evaporate to dryness upon the water-bath. Reduce the residue in a hot mortar to as fine a powder as possible, extract three or four times in an Erlenmeyer flask for thirty minutes with 70-mil portions of chloroform and filter hot. Distill each portion of chloroform upon the water-bath and use the solvent again. Pass a gentle stream of air through the flask, until there is no odor of chloroform. Dissolve the residue in 10 per cent ammonium hydroxide solution and filter. Evaporate the filtrate to dryness in a weighed platinum dish, dry the residue to constant weight and deduct the weight of ash from the weight of total alkaloids. Caffein and theobromin can be separated by cold benzene, theobromin being soluble only to the extent of 1 : 100,000, whereas caffein passes easily into solution.

Method of Kunze.—Heat 10 grams of powered cacao-seeds twenty minutes with 150 mils of 5 per cent sulphuric acid. Filter while hot and add excess of sodium phosphomolybdate to the warm filtrate. Set aside for a day and wash the precipitate upon a filter with 5 per cent sulphuric acid. Decompose the moist precipitate, containing theobromin, in a large beaker with barium hydroxide. Precipitate excess of barium hydroxide by carbon dioxide, evaporate the mixture to dryness upon the water-bath and extract the well-dried residue under a reflux condenser with boiling chloroform. Evaporate the chloroform solution in a weighed flask and dry the residue to constant weight. This residue consists essentially of theobromin mixed with some caffein. This gives the weight of total alkaloids. To estimate theobromin, dissolve the residue in water containing ammonia, add excess of N/10 silver nitrate solution in known quantity and heat to boiling. This will precipitate the silver salt of theobromin ($C_7H_7N_4O_2Ag \cdot 1\frac{1}{2}H_2O$) free from caffein. Determine excess of silver in an aliquot portion of the measured filtrate by titration with N/10 sulphocyanate solution. Caffein does not form a silver compound. To determine the corresponding quantity of theobromin, multiply the weight of silver in the precipitate by 1.66.

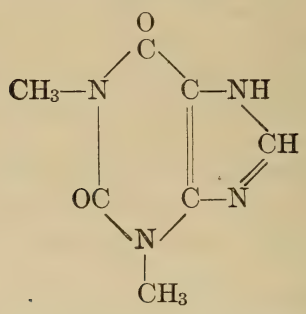
Determination of Theobromin and Separation from Caffein. (Brunner and Lewis.)—The substance, such as coffee, kola, cocoa, or maté, is boiled for thirty minutes, with 500 mils of water, under a reflux condenser. The solution is then precipitated with freshly prepared lead hydroxide, until colorless, heated again to boiling for fifteen minutes, and filtered. The residue is washed twice with 500 mils of water, the filtrate and washings being reduced, by evaporation, to a volume of 500 mils. Carbon dioxide is led through the boiling solution, the precipitated lead

carbonate is filtered off, and the filtrate evaporated on the water-bath, after adding some quartz sand. The residue obtained is extracted for eight hours with ether in a Soxhlet apparatus. After distilling off the ether, the residue is boiled out three times with 50 mils of water, and filtered, when cooled to 50° C. On evaporating and drying at 80° C., the two alkaloids are obtained as a white ash-free product.

Separation.—The mixed alkaloids are dissolved in hot water, precipitated with silver nitrate, the precipitate redissolved in 2 to 3 mils of ammonia, and the solution warmed to expel the latter, dust and a strong light avoided. After cooling to 30° C., the precipitated silver-theobromin is collected on a weighed filter, washed, and dried at 100° C. The substance has the formula $C_7H_7AgN_4O_2$.

The filtrate is treated with sodium chloride, filtered and evaporated on the water-bath. The caffein is extracted from the residue with ether, the latter is evaporated, and the alkaloid dried at 100° C,. and weighed.

Theophyllin



1-3 dimethyl 2-6 dioxypurin

Theophyllin is an isomer of theobromin and occurs in tea leaves. It is also made synthetically and marketed under the name of Theocin.

It is a powerful diuretic, and is also used in cardiac affections and dropsy.

It crystallizes in plates, melting at 264–268° C., somewhat soluble in cold but readily in boiling water, soluble in chloroform, little soluble in alcohol, and insoluble in ether,

It is a weak monoacid base and forms readily soluble potassium, sodium, and ammonium salts, and is not removed readily by solvents from alkaline solution.

It forms a crystalline hydrochloride, nitrate, chloroplatinate, aurochloride, and mercuro-chloride. When evaporated with chlorine water, theophyllin yields a scarlet residue which is changed to violet on addition of ammonia.

The silver derivative, $C_7H_7AgN_4O_2$, is obtained as an amorphous precipitate on adding silver nitrate to an aqueous solution of theophyllin. It crystallizes from hot ammonia, and dissolves readily in nitric acid. The methyl derivative, $C_7H_7MeN_4O_2$, prepared by heating the last substance with methyl iodide and methyl alcohol, melts at 229°, and is identical with caffein.

When a solution of theophyllin in sodium hydroxide is treated with a solution of 0.5 per cent sulphanilic acid and 5 per cent hydrochloric in water, followed by a few drops of 0.5 per cent solution of sodium nitrite, a red coloration is produced. Caffein and theobromin do not respond to this reaction.

It gives a precipitate with tannic acid soluble in excess of the reagent.

Theophorin is a mixture of molecular amounts of theophyllin and sodium formate.

Hypoxanthin or Sarcin

6–oxypurine

This body differs from xanthin only in possessing one less oxygen atom.

It occurs in both the animal and vegetable kingdoms and in the former is probably a decomposition product of nuclein.

It is present in the seeds of the lupine, barley, mustard, black pepper, vetch, gourd, alfalfa, cloves, in wheat bran, potatoes, sugar-beets, and tea.

It forms microscopic needles decomposing without melting at 150° C. Little soluble in water; scarcely soluble even in hot alcohol and insoluble in ether.

It possesses both acid and basic properties and combines with one equivalent of an acid and two of a base.

On oxidation with potassium chlorate and hydrochloric acid it gives alloxan and urea the same as xanthin.

It forms crystallizable salts with acids and the microscopic appearance of the nitrate and hydrochloride are characteristic.

The silver oxide compound, $Ag_2OC_5H_5N_4O$, is formed as a gelatinous precipitate on adding ammonio-nitrate of silver to an ammoniacal solution of the base. It is insoluble in ammonia, unless used in great excess, and it dissolves with difficulty in boiling nitric acid; 1.10 sp. gr. On cooling a compound of the formula, $C_5H_5N_4OAgNO_3$, separates in crystals having a characteristic form under the microscope. The character of silver nitrate compound permits the separation of hypoxanthin from other bases of the group.

On treatment with hydrochloric acid and zinc it gives a ruby-red coloration on the addition of caustic soda in excess. Adenin gives a red color under similar conditions.

Guanin

2–amido 6–oxypurin

Guanin occurs in the seeds of several leguminous plants, in those of the gourd, in the sugar-beet and in cane sugar.

It crystallizes from ammonia in needles or small plates which are insoluble in water, alcohol, or ether. It is neutral and dissolves in both acids and alkalies to form salts in which it functionates on the one hand as a diacid base and on the other as a dibasic acid.

It may be heated to 200° without change.

Guanin is distinguished from xanthin and hypoxanthin by its insolubility in hot dilute ammonia.

It gives a highly insoluble precipitate with picric acid.

It gives precipitates with potassium bichromate and potassium ferricyanide, differing thereby from xanthin and hypoxanthin.

Its hydrochloride and nitrate have characteristic forms when viewed under the microscope.

Adenin

6–amidopurin

Adenin occurs in the pancreas of the ox, in tea, and in sugar-beets. It is formed during the decomposition of nuclein by sulphuric acid.

It crystallizes in long needles with one molecule of water. The anhydrous alkaloid melts without decomposition at 360–365° C.

It is readily soluble in hot water, little soluble in cold water or alcohol, and insoluble in ether and chloroform. It is neutral and forms salts with one equivalent of an acid or a base.

Adenin does not give the ordinary color reactions of the xanthin bases, but resembles hypoxanthin in giving a red color when treated with hydrochloric acid and zinc and subsequently with an alkali.

It gives precipitates with potassium ferrocyanide and ferricyanide after acidulating with acetic acid. With chromic acid it gives a crystalline compound, and with copper sulphate an amorphous grayish-blue precipitate.

Adenin is very completely precipitated by copper sulphate in presence of a reducing body and by using sodium thiosulphate and operating in cold solutions it may be separated from hypoxanthin.

Carnin, $C_7H_8N_4O_3$, Vernin, $C_{16}H_{20}N_8O_8$, Pseudoxanthin, $C_4H_5N_5O$, Heteroxanthin, $C_6H_6N_4O_2$, and Paraxanthin, $C_7H_8N_4O_2$, are of no special interest to the drug chemist.

With the exception of caffein, theobromin, and theophyllin, all of the xanthin bases are insoluble in ether and chloroform.

They all give white precipitates with phospho-molybdic acid, mer-

curic chloride, and ammoniacal lead acetate, and guanin and adenin are very perfectly precipitated by picric acid.

A general reaction of the xanthin bases (including uric acid) is their precipitation from ammoniacal solutions by ammonio-nitrate of silver, as a gelatinous compound of the base with agentic oxide. The xanthin compound contains $C_5H_4N_4O_2Ag_2O$. The precipitates are usually insoluble in ammonia, unless concentrated and used in large excess, but to ensure complete precipitation excess should be avoided. On treating the precipitates with dilute nitric acid of 1.10 sp. gr., they are converted into compounds of the bases with silver nitrate, xanthin forming $C_5H_4N_4O_2AgNO_3$. These compounds are well-defined crystallizable bodies insoluble in water, and, in the cases of hypoxanthin, carnin, adenin, and episarkin, insoluble in nitric acid of the above strength, even on boiling; or, at any rate, crystallizing out rapidly on cooling. Guanin, carnin, adenin, and episarkin are stated by G. Salomon to behave similarly but, according to J. L. W. Thudichum, the silver nitrate compound of guanin dissolves tolerably easily in hot dilute nitric acid, and is only very gradually deposited on cooling. The compounds of xanthin, heteroxanthin, and paraxanthin remain in solution after cooling, which difference of behavior permits of their separation from the bases previously mentioned. The bases are all completely reprecipitated as their silver-oxide compounds on neutralizing the nitric acid solution by ammonia. Heteroxanthin and paraxanthin may be separated from xanthin by taking advantage of the limited solubility of their sodium salts in caustic soda, and from each other by utilizing the sparing solubility of the hydrochloride of heteroxanthin.

Mixtures of the bases with Fehling's solution and hydroxlyamin hydrochloride added all give precipitates except caffein and theobromin.

CHEMISTRY OF THE BOTANICAL INDIVIDUALS CONTAINING THE XANTHIN BASES

Phytochemical studies of some of the caffein-bearing drugs have demonstrated that in the plant the caffein is combined with acidic or phenolic-like bodies. These combinations are termed tanoides by some authors. In coffee the combination is one of caffein with chlorogenic acid and potassium, and in kola and guarana the caffein is united respectively to kolatin and guaranatin. The caffein in these combinations cannot be obtained by extraction directly with chloroform, but only after treatment with an aqueous solution.

Potassium-caffein chlorogenate can be obtained by percolating raw coffee with absolute alcohol. The first portion of the percolate is diluted with 96 per cent alcohol until a precipitation of shiny material is complete.

The clear liquid is then mixed with the remainder of the percolate, the alcohol recovered *in vacuo* and the residue evaporated to a syrup in the water-bath. The potassium-caffein chlorogenate is allowed to crystallize and the crude material recrystallized from 60 per cent alcohol. In order to obtain pure chlorogenic acid the substance is dissolved in water, enough sulphuric acid added to convert the potassium into sulphate, the liquid extracted with chloroform to remove the caffein, and then allowed to evaporate spontaneously until the chlorogenic acid crystallizes. The pure substance melts 206–207°, slightly soluble in water and ethyl acetate, readily in alcohol and acetone, practically insoluble in ether, chloroform, and carbon bisulphide. It gives a grass-green color with ferric-chloride, and a yellowish red with potassium hydroxide, darkening on exposure.

KOLA

Considerable work has been done on the constituents of this drug. Knebel first reported kolanin in 1892.[1] Hilger in 1892 and 1893 verified Knebel, the body being apparently a glucoside splitting up under the influence of heat or ferments into glucose, caffein and tannin. Carl Schweitzer continued and verified this work in 1895. Schlotterbeck published a monograph on cola in 1894. A partial analysis of cola was made by Knox and Schlotterbeck in 1895.[2] A short historical summary of the above work is given by Knox and Prescott.[3] Knox and Prescott investigated the caffein compound in cola and determined that it was a cola tannate of caffein instead of a glucoside. The question arose as to whether the tannin in this compound was identical with the free tannin in cola. Preliminary investigations seemed to show that there was a difference. They finally established the identity of the tannin combined with the caffein and the free tannin existing in cola nuts. They do not agree with Knebel's claim that the tannin of the cola is an oxidation product of cola red.[4]

Gorris isolated from fresh nuts .3 to .4 per cent of a new constituent which he calls kolatin.[5] After a critical review of the constituents Perrot and Gorris conclude that only three well-defined bodies have been isolated from the drug, namely, caffein, theobromin and kolatin. The last named has been obtained from fresh seeds in small white-colored crystals of the formula $C_8H_8O_4$. It is slightly soluble in water and its solution has the property of dissolving caffein and theobromin, as solutions of sodium and salicylate do; under suitable conditions of high oxidation, it yields cola

[1] Apoth. Zeit., 7, 112.
[2] P. A. P. A., 1895, 334.
[3] P. A. P. A., 1896, 136.
[4] P. A. P. A., 1896, 136, 1897, 131
[5] Phar. Zeit., No. 11, 1906, 118; P. A. P., A. 1906, 770.

red. Kolanin is only a mixture, probably mechanical, of cola red and caffein. It is not glucosidal and cannot be considered one of the constituents of the seeds. On drying the nuts kolatin disappears.[1] Gorris and Chevalier have studied the physiological activity of kolatin prepared from fresh cola nut and find that injected intravenously into warm-blooded animals it increases the energy of cardiac contractions and slightly raises the blood pressure. It is to a certain extent antagonistic to caffein both as regards the action on the muscles and on the central nervous system. Hence the powdered seeds sterilized before they were dried have a physiological action different from that of the dried seeds in which the kolatin no longer exists, it having been converted into cola red.[2]

Konig gives the following analysis of cola nut:

	Per Cent
H_2O	11.23
Nitrogenous material	8.34
Caffein	2.09
Theobromin	0.023
Fat	0.52
Starch	42.72
Gums and sugar	18.94
Kola red	1.29
Cellular material	10.80
Ash	3.13
	99.08

KOLATIN

Kolatin-caffein has been isolated from the fresh sterilized kola nuts. In the dry state this body does not give up its caffein to chloroform, but if dissolved in warm water the caffein may be removed by chloroform, leaving the kolatin, which crystallizes on cooling. It may be purified by recrystallization out of ether. It forms white microscopic needles, melting at 148°, slightly soluble in water, very soluble in ethyl and methyl alcohol, acetic acid, acetone, slightly soluble in ether and insoluble in chloroform and petroleum ether. It has no action on polarized light. With ferric chloride it gives a green color, becoming red with ammonia or sodium hydroxide and violet with sodium carbonate.

It is not an acid. it does not neutralize bicarbonates. It reduces ammoniacal silver nitrate in cold, and Fehling's solution on heating, and is precipitated by lead acetate, potassium bichromate, and copper acetate. It is rapidly transformed to a red amorphous body by the action of light, heat, or an oxidizing ferment, and continually loses weight when dried in a vacuum over sulphuric acid or in an oven at 105°.

[1] Pharm. Gorris, 1908, 31 and P. A. P. A., 1908, 228
[2] P. A. P. A., 1908, 414.

It has not been settled definitely whether the kola nut contains a compound of kolatin and caffein similar to the chlorogenate of caffein and potassium, or whether the kolatin compound is a complex glucoside. Kolatin is a body of the catechin group described as decomposing into phloroglucin and protocatechuic acid. Chlorogenic acid acts in similar manner.

Kola nuts contain an oxydase which acts on kolatin during drying and produces a "red." The dried nuts, representing the commercial drug contain no kolatin, hence this body will not be found in galenical preparation.

ERGOT ALKALOIDS

Ergot of rye is the sclerotium of Claviceps purpurea (Hypocreaceæ), a fungus having two distinct periods in its life history, an active and a resting stage. During the latter it forms a compact mycelium or sclerotium, which replaces the flowers and the grains of rye. It is gathered by hand or by threshing. It deteriorates with age, particularly when powdered.

The drug is produced in Russia, Spain, and Germany. Spanish ergot consists usually of large grains, having a fine appearance, but often not so active as that from other sources. It has a heavy odor which is increased when the powder is triturated with warm alkali hydroxide.

Ergot has a specific action on the uterus and is an indispensable drug to the obstetrician. The extract is an important commodity, and many modifications are offered, usually under some copyrighted name suggestive of the derivation of the product, and claiming to be more or less free from the inert and irritating substances present in the drug. Sterilized aqueous decoctions of the active ingredients free from fat and other principles are dispensed in sealed tubes for hypodermic use. In this form of package the potency of the drug is retained over a considerable period.

Solid extract of ergot is a component of emmenagogue formulas which contain, in addition, some or all of the following drugs; extract of cotton root bark, black hellebore, savine, aloes, ferrous sulphate, and oil of pennyroyal. It is also combined with Digitalis and quinin; with lupulin, atropin, Scutellaria, and zinc bromide; with gallic acid and hydrastin; with Cannabis sativa, etc. Liquid mixtures contain ergot with Caulophyllum, savine, and water pepper; and occasionally some of the drugs mentioned above.

The chemical composition of ergot has been the subject of much study. In the aggregate the discovery of a large number of the constituents has been reported, and confusion has resulted owing to the numerous designations given to the same body by different workers. It is tolerably certain that three bases at least are present—ergotinin, $C_{35}H_{39}O_5N_5$, the

hydrate of which, ergotoxin, $C_{35}H_{41}O_6N_5$, has a powerful physiological action; tyramin or hydroxyphenylethylamin, $OH \cdot C_6H_4 \cdot CH_2CH \cdot NH_2$, an important heart stimulant; and isoamylamin, $(CH_3)_2CHCH_2CH_2NH_2$. The drug also contains a coloring substance which is of great assistance to the analytical chemist for purposes of identification. Ergot contains about 30 per cent of fixed oil and fat.

Ergotinin, $C_{35}H_{39}O_5N_5$

Ergotinin crystallizes in long needles which, when subjected to the temperature of a bath at 210° and further heated, sinter, darken, and melt up to 229°. It is soluble in alcohol, acetone, ethyl acetate, and chloroform; moderately soluble in ether, benzole, and amyl alcohol, and nearly insoluble in petroleum ether. When boiled in dilute phosphoric acid ergotoxin phosphate is formed.

Ergotinin is removed from alkaline solutions by ether. A solution of this alkaloid in sulphuric acid gives with ferric chloride an orange-red color, becoming deep red, with a blue to bluish green margin. A solution in glacial acetic acid, to which ferric chloride is added and cautiously treated with sulphuric acid, will yield a violet zone at the point of contact.

Ergotinin is probably the cornutin of some investigators.

Ergotoxin, Hydro-Ergotinin, $C_{35}H_{41}O_6N_5$

Ergotoxin is a light white powder, which begins to soften at 155° and melts gradually at 162–164°. It is more soluble in organic solvents than ergotinin, though only slightly in ether, and more sensitive towards alkaloidal reagents. When boiled with acetic anhydride a molecule of water is split off and ergotinin results. Solutions of both ergotinin and ergotoxin are fluorescent.

Para-hydroxyphenylethylamin. Tyramin, $OH \cdot C_6H_4 \cdot CH_2CH_2NH_2$

This base can be extracted from ergot extracts only with great difficulty on account of its ready solubility in water. It may be removed by amyl alcohol from a concentrated solution made alkaline with sodium carbonate. When crystallized from alcohol it forms hexagonal leaflets, melting 161°. It is soluble in 10 parts of boiling alcohol, somewhat less soluble in boiling water, and still less in boiling xylol.

When treated with methyl iodide, a quaternary iodide is obtained which is identical with the methiodide of hordenin.

Barger and Dale isolated an active principle from ergot, the relative abundance of which suggested that it was wholly or partly produced by micro-organisms. They isolated the base by means of Kutscher's [1]

[1] Z. Unters. Nahr. Genussm., 1905, 10, 528; 1906, 11, 582.

method and obtained the silver compound. The hydrochloride, picrate melting 220–230°, and picrolonate melting 250° were prepared, and the base gave Pauly's reaction with *p*-diazobenzenesulphonic acid. The investigators consider that the new base is *β*-iminazolylethylamin.

Ergot contains an undetermined substance which has been called ergoxanthein or ergot-yellow by Wengell, and which is of importance in identifying the drug. It may be separated by treating an evaporated alcoholic extract of the preparation with water, filtering, washing the undissolved material with water, and extracting the filtrate first with chloroform and then with ether, the latter removing the ergoxanthein. It is an orange-yellow substance soluble in alcohol, ether, benzol, ethyl acetate, amyl alcohol, acetone, and carbon bisulphide. A residue of the separated substance is practically insoluble in water and chloroform. It gives a dark-orange color with concentrated nitric acid. It is precipitated from alcoholic solution by basic lead acetate and phosphotungstic acid, but not by barium chloride. Its alcoholic solution becomes blood red when rendered strongly ammoniacal and gives a characteristic absorption spectrum.

This test is probably the same as tnat described by Schmidt, who designates as sclererythrin a pigment existing in the outer coat of the ergot. It is an amorphous red powder, sublimable, soluble in alcohol and glacial acetic acid, slightly in ether, and insoluble in water and petroleum ether. It dissolves in ammonia, alkali hydroxides, carbonates, and bicarbonates with a red or red-violet color. An ethereal solution colors sodium hydroxide a deep red and the colored solution shows characteristic absorption bands. Sclererythrin gives blue-violet precipitates with solutions of calcium hydroxide, barium hydroxide, and lead acetate. Iron chloride produces a deep-green precipitate, and chlorine or bromine a lemon-yellow.

In working with mixtures an evaporated alcoholic extract of the sample is treated with tartaric acid and digested with alcohol, the alcohol filtered, evaporated, and the residue treated with ether. The ether is filtered into a separator and shaken with 1 to 2 c.c. of cold saturated sodium bicarbonate solution, which becomes violet if sclererythrin is present. If the ether solution be shaken with ammonia, the alkaline liquid separated and precipitated with basic lead acetate, the precipitate will color a cold saturated borax solution a red-violet color.

ALKALOIDS OF THE CALABAR BEAN

Physostigmin, $C_{15}H_{21}N_3O_2$.
Physovenin, $C_{14}H_{18}N_2O_3$.
Eseramin.

The drug yielding the above mentioned alkaloids is the ripe seed of Physostigma venenosum (Fabaceæ), commonly known as Calabar Bean.

The plant is a tall creeper and the seed is contained in long pods, two or three kernels occurring in each. The fallen seeds are collected by the natives and used by the medicine men in their ordeal tests, from which these seeds have derived the name of "ordeal bean."

The drug is official in the several pharmacopœias, but it is probable that the seeds from other species of Physostigma are sometimes substituted for P. venenosum in the preparation of medicinal products.

The drug is rarely used in medicine, but physostigmin salicylate and sulphate are employed in tablet form and usually unaccompanied by other agents. An extract of the drug is sometimes combined with belladonna, colocynth, and Podophyllum. Physostigmin is dispensed with pilocarpin and is often used in veterinary practice for colic in horses. The alkaloid may be anticipated in remedies used in traumatic tetanus, strychnin poisoning, muscular rheumatism, spinal menengitis, torpid constipation, and chronic bronchitis. It is a powerful myotic.

Physostigmin

Physostigmin, also known as eserin, crystallizes from a mixture of benzol and petroleum ether in prisms melting 86–87°. It is dimorphous, the modification melting 105–106°. Both modifications are lævorotatory to the same degree $(\alpha)_D -$ 75.8°. Physostigmin is slightly soluble in water and petroleum ether and dissolves readily in the other organic solvents. It yields precipitates with most of the common alkaloidal precipitants, but with platinic chloride, mercuric chloride and potassium chromate precipitation occurs only when the solution is concentrated, and potassium iodide and ferrocyanide give no precipitate. A purplish-brown precipitate is thrown down with gold chloride and the solution turns brown, becoming red in ten to fifteen minutes. The platinum compound melts at 180° C. with decomposition, the gold salt at 163–165°.

When a solution of physostigmin is treated with a slight excess of ammonia, alkali or alkali carbonate, a pink color develops at once, due to oxidation and formation of rubreserin. If a solution is oxidized in the presence of potassium hydroxide and oxygen and then just neutralized with sulphuric acid, the rubreserin can be extracted with chloroform and left as a deep red substance on evaporating. Its formula is

$$C_{13}H_{16}O_2N_2 \cdot H_2O.$$

Another interesting oxidation product is eserin blue, which is formed when an alcoholic solution of physostigmin is treated in a flask with an aqueous solution of barium hydroxide and about one-quarter the volume of air. The red color first obtained soon changes to green and then to blue when more air is admitted, and the addition of air may be repeated until a deep blue solution is obtained. The oxidation product is soluble

in chloroform and may be extracted from the latter with dilute hydrochloric acid.

Physostigmin gives a yellow color with concentrated sulphuric acid, soon turning orange; on adding potassium iodate a purple tint is produced changing to yellowish red; with nitric acid a blood-red residue turning green is obtained on evaporation, and the subsequent addition of alcoholic potash produces a brownish-green solution, with a momentary purple shade in thin layer, the solution becoming green on the subsequent addition of acetic acid; Froehde's reagent gives a violet color, turning brown. Hot ammonia added to a physostigmin residue produces a yellowish-red solution, on evaporation a blue or blue-green residue is left, soluble in alcohol to a blue solution which becomes violet-red and fluorescent on adding acetic acid.

Physostigmin forms well-defined salts of which the sulphate, salicylate, benzoate, and hydrobromide are best known. The salicylate is soluble 1–70 or thereabout in water and may be obtained as a precipitate by adding sodium salicylate to a concentrated neutral solution of the sulphate. The picrate melts 133° C.

The composition of physostigmin has been studied by Salway,[1] but the work is not completed. By alkaline hydrolysis eserolin is obtained according to the equation

$$(C_{13}H_{16}ON)NH \cdot CO \cdot NH \cdot CH_3 + H_2O = C_{13}H_{16}ON \cdot NH_2 + CO_2 + NH_2CH_3.$$

Eserolin is a strong base, probably an indole derivative.

Physovenin

This is a weak base discovered by Salway [2] in his researches on the Calabar bean. It is moderately soluble in ether and readily in alcohol, benzol, and chloroform. It dissolves in strong mineral acids but is again precipitated on dilution. It precipitates barium carbonate from a solution of barium hydroxide, and the solution becomes red. Salway believes that physovenin is an intermediate product in the conversion of physostigmin into eserolin. It is a powerful myotic.

Previous investigators have reported the presence of bases called isophysostigmin and eseridin in Calabar beans, but Salway was unable to find any substances answering their description.

Eseramin

This alkaloid, which was found by Salway in very small amount in the Calabar bean, is sparingly soluble in ether, chloroform, and benzol

[1] Trans. Chem. Soc., 1912, Vol. 101; 1913, Vol. 103.
[2] Ibid., 1911, Vol. 99.

and readily in alcohol. It is apparently left behind in an ethereal solution on shaking with weak acid, but dissolves in strong mineral acids and gives a precipitate with Mayer's reagent.

Geneserin

A base to which this name has been given and having the formula $C_{15}H_{21}O_3N_3$, was reported by Polonovski.[1] He obtained it by extracting the beans with ether in the presence of sodium bicarbonate. The ethereal solution was shaken out with sulphuric acid, the alkaloids liberated with bicarbonate, extracted with ether and the solvent evaporated. The residue was oily and on standing the geneserin crystallized. From the residual oil the physostigmin was separated by the addition of salicylic acid.

The identification of physostigmin in medicinal products presents little difficulty. In the customary scheme of analysis it will be obtained on shaking out an alkaline solution with ether and its presence will have been suspected by the pink color which appears when the acid solution is made ammoniacal. The residue should be separated into several fractions and the different color tests applied. If desired a physiological test may be conducted by applying a solution of the base to the eye of some animal having a large pupil.

A quantitative determination is best made by crushing a number of tablets, and introducing the powder into a separator, moistening with water, rendering slightly acid and then adding a slight excess of sodium bicarbonate. The physostigmin can then be extracted by shaking ten times with small quantities of ether, the solvent combined, washed with water, filtered into a tared dish, evaporated and the residue weighed.

ALKALOIDS OF PAREIRA ROOT

The root of Chondrodendron tomentosum (Menispermaceæ) yields the drug Pareira Brava. The plant is a perennial climber, native of Brazil and Peru. The drug is often substituted by, and sophisticated with other roots, some of which include C. platyphyllum, Stephania discolor, white pareira from Alrita rufescens, yellow pareira from A. amara, and false pareira from Cissampelops Pareira.

The extract of the drug is used as a tonic, aperient, and diuretic, and may be suspected in medicines recommended for affections of the kidneys, leucorrhea, dropsy, rheumatism and jaundice.

The alkaloid bebeerin, $C_{16}H_{13}O(OH)_2(OCH_3)NCH_3$, has been identified among the bases of Pareira barva, and has been studied to some extent by Scholtz,[2] who finds that it exists in two forms, one of which is crystalline, melting 214°, when obtained from methyl alcohol, and the other amorphous, when obtained from other solvents. Scholtz found

[1] Bull. Soc. Chem.. 17. 235.

[2] Arch. Pharm., 244, 555.

that on extracting the drug with dilute sulphuric acid and adding sodium hydroxide, he obtained a brown resinous mass yielding about 10 per cent of amorphous bebeerin when extracted with ether. By extracting the remaining insoluble mass with pyridin and precipitating with methyl alcohol he obtained a nearly white powder of the same composition and nearly the same properties as bebeerin, but differing from it in being less soluble and melting at 300°. A crystalline alkaloid which he had previously isolated had an optical rotation of −298°, while the base extracted above gave a rotation of +297°. In other respects they were identical, both melting 214°. When concentrated chloroform solutions of these two bases were mixed they soon became turbid and a precipitate settled out which, on drying, was found to melt at 300°. The two active forms are soluble in acetone and chloroform while the product of the ether mixture noted above is practically insoluble. Scholtz concludes that the new compound is the racemic form of the alkaloid, and that sometimes one and sometimes the other form of the alkaloid may predominate in the plant. The active forms do not change to the racemic form by the action of solvents or the chemicals used in the separation of the alkaloids from the drug.

The alkaloidal residue from Pareira gives a purple color with concentrated nitric acid.

Scholtz [1] also obtained from Pareira a base which he calls chondrodin. It is soluble in dilute acids and alkalies, but not in the ordinary organic solvents except alcohol and aniline. Like bebeerin it is very easily oxidized, but it differs from bebeerin in giving no characteristic color tests.

The composition of the greater portion of the basic residue obtained from Pareira is as yet undetermined owing to its tendency to resinify. The bases thus far isolated oxidize with ease, and it is probable that their transformation products make up the larger portion of the alkaloidal content of the drug. Commercial bebeerin sulphate probably consists in large part of these transformation products.

Faltis [2] has worked with commercial bebeerin sulphate, and from it claims to have extracted several alkaloids more or less similar to the bebeerin of Scholtz.

CACTUS ALKALOIDS

Anhalin, $C_{10}H_{17}NO$.
Mescalin, $C_7H_5(OCH_3)_3N \cdot CH_3$.
Anhalonidin, $C_{12}H_{15}NO_3$.
Anhalonin, $C_{12}H_{15}NO_3$.
Lophophorin, $C_{13}H_{17}NO_3$.
Pellotin, $C_{10}H_{10}O(OCH_3)_2N \cdot CH_3$.
Anhalamin, $C_{11}H_{15}NO_3$.

[1] Arch. Pharm., 249, 408. [2] Monats. Chem., 1912, 33, 873.

These bases occur in several species of Lophophora and Anhalonium (Cactaceæ) growing chiefly in Mexico. The dried tops of L. williamsii and L. lewinii constitute the drug, and are more or less button-shaped, accounting for the name mescale button, the term commonly used in designating the product. The drug is a powerful sedative and cardiac tonic. It is seldom used in this country and at the present time the importation is forbidden.

Lophophora lewinii contains mescalin, anhalonidin, anhalonin, lophophorin, anhalamin, and possibly pellotin.

L. williamsii contains pellotin and probably the other bases mentioned.

Anhalonium fissuratum contains anhalin.

Anhalin

Anhalin forms stellate masses of white prisms, melting 115°, slightly soluble in cold water, more so in hot water, and very easily in alcohol, methyl alcohol, ether, chloroform and petroleum ether. When dissolved in concentrated sulphuric acid and treated with a drop of nitric, a green color is produced.

Mescalin, $CH_3 \cdot NH \cdot CH_2 \cdot C_6H_2(OCH_3)_3$ (1 : 3 : 4 : 5)

Mescalin crystallizes in small white needles, melting at 151°, readily soluble in water, benzol, chloroform, and alcohol, but only slightly in ether and petroleum ether. It gives precipitates with the usual alkaloidal reagents.

Mescalin was reported by Heffter [1] to form small white needles softening at 105° and melting 150–160°, but later he found that it was an oily liquid which absorbed carbon dioxide, forming a crystalline carbonate.

The base is soluble in water with a strong alkaline reaction; the aqueous solution expels ammonia from its salts and precipitates the hydroxides from copper, lead, and zinc salts.

The alkaloid produces intoxication, the user experiencing remarkable color visions.

Anhalonidin, $(CH_3O)_2(OH)C_{10}H_7 : NH$

Anhalonidin crystallizes in small yellow needles, melting 160°, and is readily soluble in water and the usual organic solvents. When recrystallized from benzol it forms small octahedra which soften at 151° and melt at 154° with discoloration. Its aqueous solution is alkaline. It is precipitated by alkaloidal reagents.

Solutions of its salts give a blue color with ferric chloride, turning green on warming and then disappearing.

[1] Ber., 1901, 34 (12) 3004.

Anhalonin

Anhalonin melts 85.5° and boils without decomposition. It is much less soluble in water than either mescalin or anhalonidin.

Lophophorin

Lophophorin separates in the form of oily drops on adding alkali to a solution of its salt. It does not crystallize.

Mescalin, anhalonidin, anhalonin, and lophophorin yield the same color reactions with sulphuric acid both alone and in presence of nitric; sulphuric gives a yellow solution, changing to violet on the application of heat; on adding nitric a deep violet changing to brown is obtained.

Pellotin, $C_{10}H_{10}O(OCH_3)_2N \cdot CH_3$

Pellotin forms hard, colorless, tabular crystals, melting 110°, slightly soluble in cold water, readily in alcohol, acetone, ether, and chloroform. When dissolved in concentrated sulphuric acid and treated with a drop of nitric, an intense permanganate color develops.

Solutions of its salts give a blue color with ferric chloride, turning green on warming and then disappearing.

Anhalamin, $C_9H_7(OCH_3)_2(OH) : NH$

Anhalamin crystallizes from absolute alcohol in spherical aggregates of microscopic needles melting at 185.5°. It is soluble in hot water, from which it crystallizes in needles.

Aqueous solutions of its salts give a blue color with ferric chloride, which turns green on heating and then disappears. Pellotin and anhalonidin give the same reaction, but not mescalin, anhalonin, and lophophorin, which contain no hydroxyl group.

Part III

GLUCOSIDES, GLUCOSIDAL DRUGS AND NATURAL DRUGS CONTAINING PRINCIPLES OTHER THAN ALKALOIDS

CHAPTER X

GLUCOSIDES

Definition

The chemistry of the glucosides is in a far less advanced state than that of the alkaloids. Many substances which were formerly looked upon as glucosides have been carefully studied and found to be mixtures of several bodies often of no glucosidal character. We are indebted to Dr. Power (late of the Wellcome Research Laboratories) and his associates for clearing up many points in this field. The work of these men in determining the actual chemical composition of drugs has been a great step in the advancement of medicinal chemistry, and as a result of their researches the list of individual glucosides has been considerably curtailed. Formerly it was customary to consider that if a plant did not contain an alkaloid or some acidic or readily recognizable ingredient, it probably contained a glucoside. And if it contained a little resin, which most plants do, this resin was given some name significant of the plant and called a glucoside. But these vague resins have now been subjected to systematic analysis and their true character determined; thus "Jalapin" and "Convolvulin," which for years held a prominent place in the chemistry of jalap, have been relegated to the mythology of our science, and many others, "leptandrin," "euonymin," "caulophyllin," "taraxacin," for example, have become tradition.

The term glucoside is applied to a substance belonging to a class of organic compounds which under proper conditions may be resolved into two stable, simpler bodies, one of which is always a sugar and the other of phenolic, acidic, alcoholic, or neutral nature. This resolution is in

the nature of an hydrolysis, the elements of water being divided between the new bodies. Glucosides are usually of high molecular weight and are composed of carbon, hydrogen, and oxygen, with sulphur or nitrogen in rare instances. They are found widely distributed in nature and can be prepared synthetically.

The resolution of the glucosides may be brought about by enzymes existing in the plant, and often by the time a drug is incorporated in a medicinal product the hydrolysis will be completed. It may also be accomplished by boiling the glucoside with water, and is readily effected by the action of hot dilute mineral acids.

The study of glucosides is concerned more with a consideration of their products of hydrolysis than with the substances themselves, because the resolution products usually can be handled and submitted to various reactions without further decomposition, while the glucosides may be in process of breaking up during the analysis, and the reactions will be complicated by the presence of the resolution products.

Glucosides are relatively indifferent substances; they do not yield salts like the alkaloids, and they are not removed from immiscible solvents by either acid or alkali. They are usually soluble in alcohol and water, and if soluble in any immiscible solvent, such as ether or chloroform, they may be removed from their aqueous solution slowly but more or less completely by these agents. As a rule the glucosides are much less soluble in ether and chloroform than in water and alcohol, and in some instances they are practically insoluble, or so little soluble that they are not removed from aqueous solution. On the other hand, while of course the sugar is usually very soluble, the other resolution product is usually much less soluble in water than the original glucoside and much more soluble in immiscible solvents, so that after hydrolysis it is separable from the acid liquid. Furthermore this resolution product often reacts with an alkali and hence may be shaken out from its solution in an immiscible solvent.

The reactions of glucosides with precipitating and color producing reagents are much less characteristic than is the case with alkaloids. They do not react with potassium mercuric iodide, and hence, in a mixture, the alkaloids can be separated without difficulty. A few of them are precipitated by tannic acid, picric acid, lead acetate and basic lead acetate, and a solution of ammonium molybdate slightly acid with hydrochloric acid. Some of them give fairly characteristic colors with sulphuric or nitric acid, but the tests that are reported have been made with impure products so often, that the chemistry in this respect is confusing.

The majority of glucosides yield ordinary dextro-glucose on hydrolysis, some rhammose, some galactose, and a few give sugars whose nature appears to be somewhat extraordinary and in some cases needs further study.

Some of the glucosides are extremely poisonous. Some give solutions which froth on agitation.

The chemistry of glucosidal drugs is intimately associated with that of the resins, and with our present knowledge of the subject it is impossible to draw a distinction between drugs whose activity depends solely on their resinous constituents, those whose activity depends on both resinous and glucosidal constituents, and those whose activity depends on glucosides alone. Again, it is probable that in many cases the activity is independent of any of these components. In this section we shall endeavor to classify the drugs according to their most prominent ingredient, and in general it will be noted that in each class the uses to which the drugs are put will be of a similar nature.

Heart Tonic Drugs and Their Glucosides—Strophanthus, Digitalis, Convallaria, Squill

THE STROPHANTHUS GLUCOSIDES

There are thirty or more species of Strophanthus, and the seeds of S. Kombé and S. hispidus are official. The seeds of other species are sold on the market and probably are often mixed with the official drug. Their active principles are glucosidal substances of an extremely poisonous nature.

On account of the extreme toxicity of this drug and of the pure strophanthin, which is also an article of commerce, they will be encountered but rarely in analytical work except in products where their presence is already declared.

Strophanthus is a powerful cardiac stimulant and has diuretic properties. The true strophanthin glucoside is a cardiac stimulant, but is reported to be without diuretic action. The drug is dispensed in the form of a tincture, the extract is made up into pills and tablets, and strophanthin is administered in tablet form. Most of the mixtures of Strophanthus or its glucosides with other drugs are intended for heart tonics, and these combinations usually contain cardiac drugs. Thus we meet with combinations of Strophanthus with Cactus grandiflorus, spartein, strychnin, nitroglycerin, and Digitalis glucosides; with spartein, codein, and caffein; with caffein, nitroglycerin, and Digitalis; with nitroglycerin and Digitalis; and to some of these combinations reduced iron or Blaud's mass may be added.

The seeds of S. Kombé contain from 2 to 3 per cent of strophanthin, a large amount of fixed oil, kombic acid, choline, trigonelline and other of the more common plant constituents.

The latex of S. glaber syn. gratus contains ouabain, which is also known

as G-Strophanthin. It is closely related to strophanthin, the latter being apparently its methyl derivative.

Pure strophanthin, $C_{40}H_{56}O_{15}+3H_2O$, crystallizes in fine white needles or long plates. Its water of crystallization may be expelled by heating *in vacuo* to 80°, and the anhydrous substance melts 178–179°. The anhydrous glucoside is hygroscopic and the crystalline form melts in its water of crystallization at about 158°. Strophanthin is readily soluble in alcohol and the solvent on evaporation leaves a resinous mass. It is soluble in water, but is not dissolved by ether, carbon bisulphide, or petroleum ether, and only slightly by chloroform and benzol. Alcohol and chloroform mixtures remove strophanthin gradually from an aqueous solution, especially if saturated with sodium chloride.

With concentrated sulphuric acid it turns dark green and then brownish. When warmed with sulphuric acid the green color changes to violet shades and finally blackish. Sulphuric acid containing phenol gives a violet color, soon becoming green. An aqueous solution froths on shaking, and gives a precipitate with tannic acid, which dissolves in an excess of the reagent. No precipitate is produced by lead acetate, basic acetate, iodin, or Mayer's reagent. Dilute nitric acid dissolves strophanthin without color, but on heating to 50° a violet color appears changing to yellowish. Liquid preparations of Strophanthus seeds will give a precipitate with lead acetate due to the presence of kombic acid.

When strophanthin is warmed with 1 per cent hydrochloric acid to 70–75° it is split up into strophanthidin and a reducing sugar, the former separating out on cooling. It may be recrystallized out of hot alcohol and contains one molecule of water of crystallization, $C_{27}H_{38}O_7+H_2O$. It fuses at about 120° in its water of crystallization to a turbid mass and is liquid at about 170°. When dried it melts 169–170°, foaming at 180° and on cooling solidifies to a mass which melts at 232°. Its specific rotation is +44.2 to +44.3. Strophanthidin may be removed from an acid solution by shaking out with chloroform. As far as has been determined it has the characteristics of a dilactone.

The character of the sugar has not been definitely settled. Some investigators claim that it is rhamnose, but others believe it to be a complex carbohydrate which on further treatment gives rhamnose, mannose and methyl alcohol.

Brauns and Closson [1] as the result of an extended research on the glucosides of Strophanthus conclude that the seeds of S. Kombé contain two glucosides, the crystalline strophanthin above described, and a closely related amorphous strophanthin of apparently twice the molecular weight. By the action of water on the crystalline strophanthin there is formed a monobasic acid strophanthin or a mixture of a monobasic acid, a dibasic

[1] Journal Am. Pharm. Ass., 1913, 489.

acid, and the original crystalline strophanthin. These three strophanthins, the crystalline, acid, and amorphous, all give the same strophanthidin on hydrolysis. Crystalline strophanthin contains neither a pentose nor a methyl pentose (rhamnose), but amorphous strophanthin contains a pentose. The hydrolysis of the crystalline substance apparently takes place according to the following reaction:

$$C_{40}H_{56}O_{15}+4H_2O=\underset{\text{strophanthidin}}{C_{27}H_{38}O_7}+\underset{\text{disaccharide}}{C_{12}H_{22}O_{11}}+CH_3OH$$

Other workers have shown that authentic seeds of S. hispidus do not contain a crystalline glucoside, but an amorphous body which is identical or closely related to the amorphous strophanthin mentioned above. Both the crystalline and amorphous acid strophanthin show the typical heart tonic response, diminished rate, and increased amplitude of the heart beat, accompanied by a small rise in blood pressure, but the activity of the amorphous acid strophanthin is less than that of the crystalline.

Ouabain, the crystalline glucoside from S. gratus, is about twice as toxic as crystalline Kombé strophanthin.

The seeds of Strophanthus hispidus have been investigated by Heffter and Sacks,[1] who reported the presence of an amorphous glucoside giving a green color with sulphuric acid and a crystalline strophanthidin.

Sieburg [2] states that the hemolytic saponin, strophanthic acid, which Kobert has previously reported as being an accidental impurity of commercial strophanthin, is contained in varying proportions up to 0.2 per cent in all varieties of the drug, from the alcoholic solution of which it may be obtained by precipitation with an acid after removal of the alcohol. The pure saponin, $(C_{21}H_{34}O_{10})_4$, is of acid nature, is precipitated from its solutions in water or alkali by picric or phosphomolybdic acid and also by concentrated ammonium sulphate and sodium chloride. It is readily soluble in aqueous alcohol, but sparingly in water. With salts of some of the heavy metals it forms precipitates of indefinite composition. On hydrolysis with acids it is resolved finally into dextrose and strophanthigenin, $(C_{12}H_{18}O_2)_23H_2O$, a sapogenol which likewise possesses hemolytic properties.

Rezzaghi[3] describes a number of color reactions which are given by strophanthin and which can be used for testing the tinctures and liquid preparations. The alcohol is evaporated, the residue diluted with water to 20 mils and divided into four parts. To (1) 2 mils pure concentrated sulphuric acid containing a trace of iron perchlorate are added, when a rose-brown precipitate is thrown down, which soon changes to green-brown. To (2) the tannin reaction is applied. To (3) a few drops of

[1] Biochem. Zeits., 40 (1912), 83. [2] Ber. deuts. Pharm. Ges., 1913, 23, 278.
[3] Bol. Chim. farm., 51–5, 149.

silver nitrate are added and on warming a deposit of metal is obtained. To (4) 2 drops of dilute sulphuric acid and a few drops of bichromate are added which produce an azure blue color.

Ouabain

Ouabain, G-Strophanthin, $C_{30}H_{46}O_{12}+9H_2O$, is obtained from ouabaio wood or from Strophanthus gratus.

It forms colorless quadratic crystals of bitter taste, easily soluble in hot water, soluble in 100 parts of cold water and 30 parts cold absolute alcohol and 30 parts amyl alcohol. It is slightly soluble in acetic ether, ether, and chloroform.

A solution of 0.01 gram in 1 mil water run onto a layer of concentrated sulphuric acid colors the latter pink to red, and the aqueous layer is colored a dirty-green color.

Heated to 105° C. it loses 20 per cent of water and the ouabain thus dried melts at 187° to 188° C.

Heating with dilute hydrochloric acid or sulphuric acid produces hydrolytic cleavage, but the strophanthidin-like substance is amorphous.

Crystallized ouabain is used in place of Strophanthus or strophanthin as a substitute for Digitalis.

Antiarin

Antiarin is a glucoside occurring in the latex of Antiaris toxicaria of Java. There are apparently two forms which have been described as alpha and beta, and their action closely resembles that of the Digitalis glucosides. They are not used medicinally.

In the general scheme of analysis using immiscible solvents, strophanthin will not be removed until the alkaline solution is agitated with the chloroform-alcohol mixture, when it will be extracted in part, and more readily if the solution is saturated with salt.

The presence in a mixture of an heart-stimulating principle is most conclusively ascertained by subjecting the same to a physiological test. For details of work of this character one must refer to works on pharmacology. Even though the presence of an heart stimulant is indicated by physiological test the identity of the principle will require substantiation by chemical means, and as strophanthin yields strophanthidin so readily on acid hydrolysis, a procedure with this end in view should be adopted and the decomposition product shaken out with chloroform and recrystallized.

In quantitative work the hydrolysis to strophanthidin and its recovery with chloroform along the lines indicated in Haycock's assay process for the seeds, can be employed to advantage. In mixtures containing alkaloids, an alcoholic extract should be evaporated and then taken up with

water or very weak acid, which is immediately made alkaline and the alkaloids shaken out with ether and chloroform. The alkaline solution is then neutralized with hydrochloric acid and an excess added up to 1 per cent, heated to 70–75° for half an hour, subsequently shaking out with chloroform to remove the strophanthidin, which can then be recovered and weighed.

THE DIGITALIS GLUCOSIDES

The leaves and seeds of several of the Digitalis species contain a number of glucosides, some of which possess marked physiological activity, affecting the heart and blood. The leaves of D. purpurea, purple foxglove, are designated as the official drug, and the seeds are used for the preparation of the commercial glucosides.

The chemistry of the plant is very imperfectly understood, several principles have been isolated in a greater or less degree of purity, but unfortunately there is a confusion of nomenclature and the same name may be applied in a commercial way to several mixtures of entirely different appearance and action. This is especially true of the term " digitalin," which is not only applied in a scientific way to one of the glucosides, but also to commercial mixtures of the glucosides. Thus we have:

Digitalinum purum, or German digitalin, a mixture of several glucosides, consisting of 50 to 60 per cent of digitonin and only 5 to 6 per cent of true digitalin. German digitalin is the preparation usually found on the market and is ordinarily dispensed when " digitalin " is prescribed.

French digitalin, or Homolle's digitalin, a mixture of several glucosides, but consisting mainly of true digitalin.

Merck's crystallized digitalin is neither digitalin nor digitoxin, but digitonin or digitin, Merck using the three terms, crystallized digitalin, digitonin, and digitin as synonyms.

Digitaline crystallisée of Nativelle is not digitalin, but is nearly identical with digitoxin.

Digitalis functionates in medicinal preparations in several forms; first as an extract of the drug prepared by simple extraction with solvents, second as a partially purified and perhaps concentrated extract which is sold under various trade names, and third as a purified or perhaps it would be more correct to say a partially purified mixture of its active principles, chiefly glucosides.

While its chief use is as a heart tonic, Digitalis is also found in diuretic mixtures, and seems to be particularly useful in dropsy and in renal obstruction.

Where the drug is dispensed in the form of its fluid, solid or powdered extract or concentration it will be found alone in pills and tablets of definite

strengths, and combined with caffein; with Squill and potassium nitrate or mercury, sometimes with the addition of buchu, juniper, or other mild diuretic; with phosphorus and Hyoscyamus; with phosphorus and iron; with phosphorus, ipecac, and opium with perhaps iron and quinin; with Cannabis sativa and iron; with nitroglycerin; with Strophanthus; with aconite; with strychnin and belladonna and sometimes in different combinations with the five last named; with ergot and quinin; with Cactus grandiflorus, spartein, Strophanthus and strychnin; with gold and sodium chloride, strychnin, atropin, nitroglycerin, and Capsicum; with sodium bromide, acetanilid, and hyoscyamin, with sodium salicylate and colchicin; with iodides, guaiac, colchicin and Phytolacca decandra; and other preparations of the same general composition.

In the form of a concentrated and partially purified extract it is generally dispensed by itself and as stated above a preparation of this type will have a name suggestive of the drug, as for instance " Digitaline," "Digatol," " Digitone," " Digitalen," etc.

The separated glucosides, which in the commercial form generally go by the name " digitalin," are dispensed in tablet triturates and hypodermic tablets of different strength. Digitalin is also combined with nitroglycerin, strychnin, and strophanthin.

The drug may be found adulterated with the leaves of mullein (Verbascum thapsus), primrose, comfrey (Symphytum officinalis), and matico (Piper angustifolium).

The chemical examination of Digitalis has resulted in the isolation of several glucosides, and while some are of doubtful identity, it seems probable that those having some claim to individuality are digitoxin, digitalin, digitonin, digitalin, and perhaps digitalein. Recently Windaus and Schneckenberger [1] have reported a new glucoside which they have extracted from German " digitalin " and to which they give the name gitonin.

Berry [2] has conducted a phytochemical research on the leaf which may be summarized as follows:

He found digitoxin, 0.1–0.3 per cent, insoluble in water, but soluble in diluted alcohol; digitalein or gitalin, 0.3–0.9 per cent, a glucoside soluble in water; two saponins, 0.6 per cent, (*a*) digitonin, amorphous, soluble in water, (*b*) gitin, crystalline, insoluble in water; a fat or resin extracted by ether, which acts as an irritant; a fluorescent body, luteolin or digitoflavone; an active enzyme or oxydase.

Digitoxin, $C_{34}H_{54}O_{11}$

Depending on the solvent from which it is crystallized, it is either hydrated or anhydrous. The hydrated form is obtained when crystallized

[1] Ber., 1913, 46, 2628. [2] Pharm. J., 1915, 95, 783.

from alcohol and the anhydrous from chloroform and alcohol mixture, forming colorless rectangular leaflets melting at 243° C.

It is insoluble in water, benzin, or carbon disulphide, slightly soluble in ether, and easily soluble in chloroform. At 15° C. it is soluble in 79.80 parts of absolute alcohol and in 43.04 parts of 90 per cent alcohol. It is slightly soluble in fatty oils.

Digitoxin dissolved in 2 mils glacial acetic acid containing a trace of ferric chloride when poured onto 2 mils of concentrated sulphuric acid containing a trace of ferric chloride, will produce a brown color at the zone of contact of the two solutions. This color gradually changes to green and finally an indigo blue; after one-half hour the entire acetic acid layer will become blue.

It dissolves to a colorless solution in cold concentrated hydrochloric acid, but when this solution is heated on the water-bath for some time a green color is obtained. Concentrated sulphuric acid dissolves it, producing a green color.

Digitoxin on hydrolysis with 50 per cent alcohol containing 1 per cent of concentrated hydrochloric acid, yields digitoxigenin, $C_{22}H_{32}O_4$, melting 230°, and digitoxose, $C_6H_{12}O_4$, the latter decomposing readily by boiling with dilute hydrochloric acid. It differs from *l*-arabinose and does not give furfurol on distillation with hydrochloric acid.

Digitoxin may be obtained from the drug as follows:

The leaves having been extracted with water, and dried, are extracted with 50 per cent alcohol. This solution is treated with lead acetate, forming a precipitate which is allowed to settle. The supernatant liquid is decanted. The remaining alcohol is evaporated *in vacuo* and the residue repeatedly extracted with ether. The ether extract is then shaken out with water and concentrated by distillation and the residue recrystallized from hot alcohol (85 per cent) and decolorized by boiling with animal-charcoal.

Digitalin

Digitalin, $C_{35}H_{56}O_{14}$, occurs as a white amorphous powder, or in characteristic, granular masses. It melts at 217° C. and becomes yellow. It is soluble in 1000 parts of water and in 100 parts of 50 per cent alcohol, but nearly insoluble in ether and chloroform. Digitalin dissolved in alcohol and treated with very dilute acid and heat yields digitaligenin and two sugars.

With concentrated sulphuric acid digitalin forms a golden-yellow solution which on the addition of potassium hypobromite solution changes to a magnificent rose red or violet red.

If dissolved in 3 to 4 mils of glacial acetic acid to which a trace of ferric chloride solution has been added and the mixture carefully under-

laid with concentrated sulphuric acid a deep carmine-red band appears; the lower layer of the acetic acid is light yellow, changing to brownish (Keller's reaction).

Sulphuric acid containing a little ferric sulphate gives at first an intense golden-yellow color, and then a red solution; this color rapidly changes to a beautiful and permanent violet. If too much digitalin is used the red color remains and only the surface layer becomes violet.

If digitalin is stirred to a thin paste with water and for every 100 parts of water used 22 parts of amyl alcohol is added with shaking, and the mixture set aside in a closed vessel for twenty-four hours, the presence of digitonin will be indicated by the formation of distinct masses of crystals.

On hydrolysis with alcoholic hydrochloric acid dextrose, digitalose, $C_7H_{14}O_5$, and digitaligenin, $C_{22}H_{30}O_3$, melting 210–212°, are formed.

Kiliani's method of preparing digitalin from German "digitalin" is as follows:

To a solution of one part German digitalin in four parts of 95 per cent alcohol, five parts of ether by weight (sp. gr. 0.720) are added and the mixture allowed to stand in a closed vessel for twenty-four hours. In the clear supernatant solution the quantity of dissolved substances is estimated and the whole then subjected to a vacuum distillation until its weight becomes 1.6 times that of the total dissolved substances. To this concentrated solution water, in an amount 2.4 times the weight of dissolved substance, is added, forming a solution containing approximately 20 per cent alcohol, from which crude digitalin gradually separates on standing. The crude product is washed first with 10 per cent alcohol and then with water, and finally dried at a moderate temperature. Further purification is effected by boiling the alcoholic solution with animal charcoal.

Digitonin

Digitonin, $C_{27}H_{46}O_{14}+5H_2O$ or $C_{54}H_{92}O_{28}$ or $C_{55}H_{94}O_{28}$, is a saponin-like glucoside and crystallizes in colorless needles or thick, warty masses which dissolve in 600 parts of cold water and 50 parts of warm water to a turbid solution, but dissolves to a clear solution in 50 parts of 50 per cent alcohol. Its solutions are lævorotatory. When heated in alcoholic solution with hydrochloric acid it is split into dextrose, galactose, and digitogenin, $C_{30}H_{48}O_6$ or $C_{31}H_{50}O_6$. It is slightly soluble in absolute alcohol and still less in ether or chloroform.

Concentrated sulphuric acid dissolves it with a red color which is intensified by the addition of a drop of bromine water, though Reichard states that there is no color with pure sulphuric acid.

Concentrated hydrochloric acid dissolves digitonin without color, but

the solutions become yellow and finally reddish-violet on heating or on long standing.

Keller's reaction gives a rose-red zone which soon fades.

Reichard has found that if an evaporated solution of cobalt nitrate is rubbed with digitonin and glacial acetic acid and allowed to stand twenty-four to thirty-six hours, rose-red transparent hexagonal crystals are formed.

Digitonin combines with a molecule of cholesterol in alcoholic solution to give a crystalline precipitate and is then readily separated from digitalin.

The presence of digitonin in aqueous infusion causes a partial solution of digitalin and digitoxin though these glucosides in the pure condition are practically insoluble in water.

Digitonin is separated from German digitalin by the addition of ether to the alcoholic solution. The precipitate is dissolved in 10 parts of 85 per cent alcohol and the solution put into water at 45° C. After standing from six to eight hours the greater part of the digitonin will crystallize out.

The researches on digitonin by Schmiederberg and Kiliani indicate that there may be two forms of the glucoside, and Kraft considers them different substances and suggests the name digitsaponin for the Schmiederberg body.

Gitalin

Gitalin is a glucoside recently described by Kraft. It is obtained from the leaves by extraction with water, and removed from the aqueous decoction by chloroform after clarification with lead. The chloroform solution, after shaking out with sodium carbonate and then with anhydrous sodium sulphate, is poured into petroleum ether whereby the glucoside is precipitated. It is an amorphous white powder permanent in the air, melting 150–153°, soluble in 600 parts of cold water which subsequently decomposes it, less soluble in hot water, readily soluble in chloroform and alcohol, and decomposed by ether and carbon bisulphide. It gives a crystalline hydrate when dissolved in alcohol and treated with water. When dried *in vacuo* and allowed to remain in contact with alcohol, acetone, or chloroform it is apparently converted into a new glucoside, melting 253°, and to which the name anhydrogitalin is given.

An aqueous solution of gitalin froths on shaking and gives a precipitate with tannin. It gives a violet color with sulphuric acid containing a trace of ferric chloride. When dissolved in glacial acetic acid containing a trace of ferric chloride and then allowed to run down onto a concentrated sulphuric acid containing ferric chloride, the acid becomes indigo and the zone of contact violet.

Gitonin

This glucoside is less soluble in 95 per cent alcohol than digitonin and can be partially separated by solvent. It decomposes at 272° C. and has $(a)_D = -50.69°$ in pyridin. When hydrolyzed by acids it yields gitogenin, a galactose, and a pentose.

Digitalein

Digitalein is a Schmiederberg product which seems to be closely related to digitonin. It is a water-soluble cardiac poison with a lactone group in the molecule. Further study seems desirable before accepting this body as a chemical individual.

COMMERCIAL PREPARATIONS

Digitalin, "French"—Homolle's Digitalin

Digitalin, French, is a mixture obtained from Digitalis purpurea by the method of Homolle, consisting mainly of digitalinum verum, Kiliani.

Powdered digitalis leaves are moistened with water and slowly exhausted in a percolator. This is precipitated with 250 parts of lead acetate and the filtrate from the precipitate treated with 40 parts of crystallized sodium carbonate and 20 parts of sodium ammonium phosphate, in order to remove the excess of lead. The filtrate is precipitated with 40 parts of tannic acid. The tannate is mixed with 25 parts of powdered litharge and 50 parts of purified animal charcoal and dried. From the dried mass the Digitalis bodies are extracted with 90 per cent alcohol, the latter is distilled off and the residue washed with distilled water and again taken up in 90 per cent alcohol. This is again distilled and the residue exhausted with chloroform. On expelling the latter the digitalin remains behind.

French digitalin is a yellowish-white, amorphous powder of a peculiar aromatic odor and bitter taste. It is neutral to litmus, almost insoluble in water, soluble in alcohol and chloroform and insoluble in ether. It softens at 90° C. and begins to melt at 100° C. It is not precipitated by solutions of lead salts; but with tannic acid, it forms a tannate insoluble in water. It is colored emerald green by concentrated sulphuric acid.

Concentrated sulphuric acid dissolves digitalin, French, producing a yellow color, which finally goes over to an emerald-green color.

Digitalin, German

Digitalin, German, is a mixture of glucosides obtained from Digitalis seeds according to the process of Walz, and consisting largely of digitonin, with digitalin verum and other glucosides.

Digitalis seeds are extracted with alcohol, the alcohol driven off, the extract diluted with water and purified by precipitation with lead acetate. The filtrate is freed from lead by sodium phosphate. From the liquid thus purified the Digitalis bodies are precipitated with tannic acid, the tannate well washed with water and decomposed with lead or zinc acetate. The digitalin thus separated is taken up in alcohol, the latter carefully distilled off and the residue washed with ether as long as it takes up anything. The digitalin purified in this way is dried at a low temperature and finally powdered.

German digitalin is a yellowish-white, amorphous powder, soluble in water and alcohol, insoluble in ether and chloroform. It is said to contain about 50-60 per cent of digitonin and 5-6 per cent of digitalinum verum, the remainder being digitalein and other glucosides.

Sulphuric acid containing a trace of ferric sulphate produces with digitalin, German, an intense golden-yellow coloration, changing to red and finally to a permanent reddish-violet.

The identification of the individual digitalis glucosides in drug mixtures is complicated by the difficulty of separating them from each other in a condition of absolute purity. It is not difficult, however, for the analyst to obtain a sufficient number of characteristic tests to assure himself of the presence of these substances in any mixture with which he is confronted. Digitoxin and gitalin are both soluble in chloroform and are removable from aqueous mixtures by that solvent, and though digitoxin alone is insoluble in water it always occurs in decoctions or extracts of the drug due to the influence of the other glucosides.

In the general scheme of analysis digitoxin and gitalin and perhaps a little digitalin will appear in the fraction obtained by shaking out the acid aqueous solution with chloroform. A portion of the residue left on evaporation of the solvent, dissolved in concentrated sulphuric acid and the acid exposed to the fumes of bromine will develop a pink or purplish-pink color, and another portion treated with sulphuric acid containing a trace of ferric chloride will develop a violet color if Digitalis glucosides are present. An aqueous solution will give a precipitate with tannin. Reactions described above in detail under the individual glucosides should then be applied.

Digitoxin and gitalin can be estimated with fair accuracy by proceeding along the lines suggested by Keller in his assay method for Digitalis, but there is no chemical method for quantitatively determining the strength of so-called "digitalin" in pills or tablets containing declared amounts of this substance or in mixtures of other drugs.

Martindale [1] describes a chemical method by which he claims it can be readily ascertained whether a tincture of Digitalis is up to the physio-

[1] Pharm. J., 1912, 35, 745 and 778.

logical requirements. Ten mils of the tincture are mixed with 10 mils of water and precipitated with 3 mils of 10 per cent lead acetate solution, a little kieselguhr being added. After standing for fifteen minutes the precipitate is filtered off and washed. The lead is removed from the filtrate by 2 mils of 10 per cent sodium phosphate and the filtrate evaporated to dryness after the addition of .2 gram calcium carbonate. The residue is mixed with sand and extracted five times with 10-mil portions of chloroform. On evaporating the chloroform the residue is extracted with 10- and 5-mil portions of water, using sand, and the filtrate evaporated to dryness and extracted with 5-mil portions of chloroform as before. The chloroform solution is evaporated and the residue dissolved in 4 mils of glacial acetic acid; 0.1 mil of the acid solution is mixed with 1 mil of sulphuric ammonium molybdate solution in a 5×1 cm. test-tube and the depth of color produced after five minutes is compared with a standard. The coloration indicates the content of combined active water-soluble glucosides.

GLUCOSIDES OF CONVALLARIA

The root and rhizome of Convallaria majalis (Liliaceæ) contain glucosidic substances resembling those present in Digitalis and possessing heart tonic and diuretic properties. The drug does not enjoy the wide range of usefulness as does Digitalis, but its presence may be suspected in the same class of preparations.

The flowers and the herb are also credited with active properties and their extracts find a place in the materia medica.

Two glucosidic substances have been isolated from the drug. One of these, convallarin, is slightly soluble in water and renders the solution acrid and frothy. It is readily soluble in alcohol. Convallamarin is readily soluble in both alcohol and water. Neither of these glucosides is precipitated by basic lead acetate, but convallamarin is thrown down by tannin and by this means can be separated from convallarin.

In working with drug mixtures, an alcoholic solution may be precipitated by lead subacetate, filtered, the excess of lead removed and the filtered liquid freed of alcohol, and precipitated by tannin, the solution being neutralized by a little sodium carbonate. The tannin compound of convallamarin is then dissolved in 60 per cent alcohol, decomposed with zinc oxide, filtered and evaporated to dryness. If contaminated with salts it may be dissolved in alcohol and filtered.

Convallamarin will be removed from an acid aqueous solution to a very slight extent by ether and chloroform, and a dry residue containing it will give a brown to purple color with concentrated sulphuric acid. The greater proportion of the glucoside will remain in solution after the

shaking out process with immiscible solvents is completed. Convallarin being but slightly soluble in aqueous liquids will be left behind in the evaporated alcoholic residue which has been extracted with water.

SQUILL

The bulb of Urginea maritima syn. Scilla maritima (Liliaceæ) furnishes the drug known as squill, which is highly esteemed as an expectorant and enters into the composition of cough syrups. It is also employed as a diuretic. The common form of croup syrup, the Hive Syrup of the Pharmacopœia contains squill, senega, and tartar emetic, and this is sometimes modified in proprietary preparations by the addition of honey and tolu and often morphin or other opiates, and vinegar. The acetic acid extract of squill is an official preparation. Powdered squill is combined in pills and tablets with Digitalis and potassium nitrate; sometimes with buchu; with ipecac and ammoniacum; with mercury mass and Digitalis; with ipecac and camphorated opium, sometimes with ammonium carbonate and senega; with white pine bark, wild cherry, senega, ipecac, Sanguinaria, opium, potassium nitrate, and methyl salicylate; with ammonium carbonate, ammonium bromide, senega, aconite, Grindelia and guaiac.

The chemistry of squill is in an unsatisfactory state. Scillain, scillatoxin, scillipikrin and scillitin, indefinite or glucosidic substances, have been reported, but none have been obtained in a condition of purity, nor have their individualitites been demonstrated.

Kopaczewski [1] claims to have isolated three substances, one possessing diuretic properties, the second a polysaccharide and the third bitter and extremely poisonous. The latter, probably a glucoside, appears to be a light, yellowish non-crystalline powder of distinctive odor, soluble in alcohol, acetone, acetic acid, and slightly in water.

Extracts of squill yield nothing characteristic in the usual examinations with immiscible solvents, and the presence of this drug is not easy to determine. Liquid mixtures containing squill are usually heavy syrups and on standing a greenish scum collects on the surface of the liquid, especially where it touches the glass of the container. The presence of acetic acid in the mixture is a further indication that extract of squill has been employed in its makeup. Neither of these indications is of much value, however, if the analyst is obliged to present the results of his investigations before a jury, especially if the opponents are unwilling to admit the composition of the product, nor can he place any dependence on physiological tests as a means of identification.

Powdered squill is used as an ingredient of rat poisons and in toxi-

[1] Compt. rend., 158, 1520.

cological investigations where the absence of other easily recognized poisons has been demonstrated, the presence of squill may be suspected.

APOCYNUM CANNABINUM. INDIAN HEMP

The roots of certain species of Apocynum (Apocynaceæ) contain a principle having a distinct emetic, diuretic, and cardiac tonic action. It was hoped that the drug could be used as a substitute for Digitalis in certain ailments, but there was considerable uncertainty attending its administration in the early days of its use and it failed to attain the reputation hoped for it. The conflicting testimony as to its physiological activity may have resulted from carelessness in selecting the species used for testing. The dog-banes and the Indian hemp resemble one another in appearance and an unskilled collector might easily mistake one for another when digging the root. There may be no significance in this explanation, however, because recent investigators on the chemistry of A. cannabinum and A. androsæmifolium have shown that they both contain the active principle referred to above. Dr. Rusby suggests that possibly A. pubescens has yielded the drug which has been favorably reported upon.

An extract of the Apocynum root is used in dropsical affections and Bright's disease. It is combined with a variety of other botanical drugs including Podophyllum, Colocynth, Hyoscyamus, Cascara, Juglans, Nux Vomica, Gentian, Taraxacum, Capsicum, and Eupatorium.

Moore, working on A. androsæmifolium and Finnemore on A. cannabinum, isolated the emetic and cardiac-tonic principle. Moore ascribes to it the formula, $C_{28}H_{36}O_6 \cdot 2H_2O$, and calls it apocynamarin, and Finnemore gives it $C_{20}H_{28}O_6$ and calls it cynotoxine. Moore thinks that the substances are probably identical, as the physiological properties studied independently were practically the same.

Apocynamarin is intensely bitter and highly toxic. The crystals from dilute alcohol melt with decomposition at 170–175°. It is soluble in alcohol and water, but is not removed from an aqueous solution by ether. It gives no precipitate with basic lead acetate. When dissolved in acetic anhydride and treated with sulphuric acid, a red color is obtained, changing to blue and green with a reddish-bronze fluorescence.

It is possible that apocynamarin is the dilactone of Kiliani's oxydigitogenic acid, $C_{28}H_{40}O_6$, or an isomeride.

Moore also isolated aceto-vanillone and its glucoside, androsin. The former is 4-hydroxy-3 methoxy acetophenone, $C_9H_{10}O_3$, melting 112-114°, soluble in alcohol and water, and removed from the latter by ether.

Androsin is a β-glucoside, $CH_3 \cdot CO \cdot C_6H_3(O \cdot CH_3) \cdot O \cdot C_6H_{11}O_5$, melting 218–220°, readily soluble in hot water and hot dilute alcohol, sparingly in cold water and absolute alcohol. It is hydrolyzed by emulsin. Its acetyl derivative melts 154°.

THE SAPONIN-CONTAINING DRUGS

The saponins form an interesting group of glucosides which are distributed widely throughout the plant kingdom. Their chemistry has not been fully developed as yet, but attention has been directed to them of late because, due to their characteristic property of producing a frothy mixture, they have been employed as foam-producing media in beverages, and some experiments have indicated that they possess considerable toxicity. Hence, investigations with the pure substances have been instituted in order to settle this point.

From a chemical standpoint, the properties of certain drugs are dependent on one or more saponin-like ingredients, though, except under certain favorable conditions, it is impossible to differentiate between the saponins, and thus identify the specific drug which is present in a mixture. The two most important drugs are the roots of sarsaparilla and senega; those of lesser moment being quillaia or soap-tree bark and the soap-wort, Saponaria officinalis. Ginseng also contains a saponin, and Digitalis contains digitonin which has the characteristics of a saponin. As was observed above, it is seldom possible to identify the drug by its saponin when in admixture with other ingredients, but the use for which the preparation is intended, and the presence of some other well-recognized constituent in the drug will sometimes aid in establishing its identity. For instance, sarsaparilla is almost always employed as an alterative and often dispensed with iodides and licorice, while senega is used as an expectorant and is accompanied by squill, ipecac, and tartar emetic, and the drug contains a small quantity of methyl salicylate.

The saponins may be divided into two groups, neutral and acid, the former being quite extensive. The acid saponins are precipitated from aqueous solution by lead acetate, and the neutral by basic lead acetate. Most of them are precipitated by barium hydroxide. From a plant decoction the tannins and coloring matter may be thrown out first by magnesium hydroxide, which does not precipitate the saponins. They hydrolyze to sugars and sapogenins; on careful decomposition some give first a primary sapogenin and sugar, and on further treatment an endosapogenin and more sugar. They unite with cholesterol, phytosterol, and lecithin. A large number, including quillaic acid, smilasaponin, sarsaponin, and parillin, belong to a series having the general formula $C_nH_{2n-8}O_{10}$, and others, including digitonin and chamælirin, to the group $C_nH_{2n-16}O_{28}$. Some secondary glucosides from saponir have the formula $C_nH_{2n-6}O_7$; several endosapogenins have the sapogenin formula $C_nH_{2n-6}O_2$, while others contain one more or one less oxygen atom.

Saponins are either soluble in cold water, alkaline water or water containing water-soluble or impure saponins. Their solutions froth strongly

when agitated, but acids and alcohol interfere with this foam-producing property. They are, as a rule, insoluble in cold absolute alcohol and the ordinary organic solvents, but dissolve in hot alcohol, especially if diluted. Their aqueous solutions reduce the salts of the heavy metals, gold and mercuric chlorides, ammoniacal silver nitrate, ferric chloride, and potassium ferricyanide, and decolorize permanganate. With copper in alkaline solution a green gelatinous compound is produced which is soluble in water. A saponin residue develops a red to violet color with concentrated sulphuric acid, especially on warming, the solution becoming fluorescent.

Saponins react with acetic anhydride to form acetyl compounds. On hydrolyzing the acetyl body with barium hydroxide and decomposing the barium compound with carbon dioxide, a saponin is recovered which, however, usually differs from the original substance by being non-toxic, though its chemical properties are unchanged. Kobert has suggested the designation sapotoxin for the poisonous saponins, reserving the name saponin for the physiologically inactive substances.

Commercial saponin is prepared from the bark of Quillaia Saponaria, soap bark, and is a mixture of quillaic acid and quillaia sapotoxin, with inert material. It is stated to consist mainly of a non-poisonous modification of the first named substance. Commercial saponin is used as an emulsifying agent in pharmaceutical mixtures.

Sarsaparilla

The drug sarsaparilla is derived from several species of Smilax, of which the U. S. Pharmacopœia recognizes four. Smilax medica, S. ornata, S. papyracea, and S. officinalis. These are woody or herbaceous vines, with short rhizomes and long roots which are the parts used in medicine. There seems to be some confusion in the botanical origin of the different classes of sarsaparilla, and the authorities are themselves ambiguous. Thus Kraemer states in one place [1] that S. officinalis yields the Jamaica variety and that nothing is known of the plant yielding Honduras sarsaparilla, yet later in his work [2] he classifies the four commercial varieties as follows: 1. Honduras, yielded by S. officinalis growing in Guatemala, Honduras and Nicaragua and exported from Honduras and Belize; 2. Para, yielded by S. paypracea, growing in the upper Amazon region and exported from Para; 3. Mexican, yielded by S. medica, growing in Mexico and exported from Vera Cruz and Tampico; and 4. Jamaica or Central American, yielded by S. ornata, growing in Colombia, Costa Rica and Nicaragua and shipped to Jamaica, whence it is exported chiefly to England. The Honduras and Mexican varieties are chiefly used in the United States, the Para to a limited extent.

[1] Kraemer, Botany and Pharmacognosy, p. 238.
[2] Ibid., p. 446.

Among the adulterations of this drug which present difficulty of identification roots derived from Philodendron species have been reported.

Sarsaparilla will be found in liquid mixtures recommended for scrofulous affections and cutaneous diseases, chronic rheumatism, secondary syphilis, and conditions following the imprudent use of mercury. It is usually a component of the so-called "Blood Tonics." These liquid preparations will contain, in addition to Sarsaparilla, Taraxacum; sassafras, guaiacum, licorice, and Mezereum; potassium iodide; sassafras, licorice, anise, and methyl salicylate; senna, stillingia, yellow dock, Podophyllum, Xanthoxylum, sassafras, licorice, potassium, and iron iodides, celery, red clover, Stillingia, cascara, blackhaw, and bromides. These types are characteristic, some preparations will include all of the ingredients mentioned in a type, and there will be, of course, others where some of the drugs are omitted.

Three saponin-like substances have been reported as occurring in sarsaparilla—parillin, smilasaponin, and sarsasaponin.

Parillin, $C_{26}H_{44}O_{10}$, is crystalline, melting 177°, $(\alpha)_D - 42°$, and forms a penta-benzoyl derivative melting 76°. When hydrolyzed, it yields two sugars and parigenin, $C_{28}H_{46}O_4$, a colorless crystalline insoluble substance. It is sparingly soluble in cold water, but dissolves readily in hot water and slightly in diluted alcohol.

Smilasaponin, $(C_{20}H_{32}O_{10})_5$, is a lævorotatory, amorphous substance, giving a penta-benzoyl derivative and a sapogenin, $C_{28}H_{46}O_4$.

Sarsasaponin, $(C_{22}H_{36}O_{10})_{12}$, is crystalline, melting 223°, readily soluble in water and absolute alcohol, and hydrolyzing to sarsasapogenin, $C_{28}H_{46}O_4$.

Power and Salway [1] working with Jamaica sarsaparilla (S. ornata), conclude that it contains but one saponin-like glucoside, sarsasaponin, to which they give the formula, $C_{44}H_{76}O_{20}7H_2O$, melting 248°, $(\alpha)_D - 48.5°$, which on hydrolysis yields one molecule of sarsasapogenin, $C_{27}H_{42}O_3$, melting 183°, $(\alpha)_D - 60.3°$ in methyl alcohol, and three molecules of dextrose. They also report a sitosterol-*d*-glucoside, $C_{33}H_{36}O_6$, melting 280.5°, sitosterol, $C_{27}H_{46}O$, melting 135–136°, $(\alpha) - 27.3°$ in chloroform; stigmasterol, $C_{30}H_{50}O$; sarsapic acid, $C_4H_2O(COCH)_2$, melting 305°, palmitic, stearic, behenic, oleic, and linolic acids, and potassium nitrate. The total quantity of matter extracted by alcohol was equivalent to about 1.25 per cent of the weight of the root. They conclude by stating that commercial smilacin, the smilasaponin of V. Schulz, is a mixture of a small amount of sarsasaponin with indefinite amorphous products.

[1] Chem. Soc. Trans., 1914, 105, 201.

Quillaja. (Soap Bark)

Quillaja saponaria is a large tree indigenous to Chile and Peru. The bark, which is removed in large pieces and deprived of its periderm or other layer, is the official drug.

The bark of Q. paeppigii is sometimes substituted for the official drug.

Soapbark is the principal source of the commercial saponin, but it finds a place in medicine as a substitute for Polygala senega.

Quillaic acid, $C_{19}H_{30}O_{10}$, is precipitated by neutral lead acetate. It may be separated from an aqueous extract of the bark, or from medicinal mixtures by precipitating as the lead compound, decomposing the latter by hydrogen sulphide in the presence of water which dissolves the quillaic acid, filtering, concentrating nearly to dryness, adding hot absolute alcohol, and then chloroform to precipitate the coloring matter. On filtering and allowing to stand the glucoside separates. It is soluble in alcohol and water, but does not dissolve in ether. It gives a dark-red color with sulphuric acid. When purified by baryta or the acetyl method any toxic properties it may have had apparently disappear, but its chemical reactions are unchanged. This may be due to the fact that the crude material occludes some sapotoxin, though the latter is supposed to be soluble in presence of neutral lead acetate.

Quillaja saponin is not precipitated by neutral lead acetate and will be found in the filtrate from the precipitation of quillaic acid. It is a toxic substance and differs from quillaic acid by giving a yellowish color with sulphuric acid, changing slowly to reddish. It is soluble in water and alcohol.

Senega. Snakeroot

The root of Polygala senega (Polygonaceæ) is a drug indigenous to the United States, and is a popular remedy for croup and diseases of the bronchial passages. It possesses expectorant and diuretic properties, and will therefore be found in preparations intended for chronic catarrh, croup, bronchitis, pneumonia, asthma, rheumatism, dropsy, and amenorrhea. An extract of the root is the form in which this drug is dispensed. It is usually combined with ipecac or squill in liquid mixture and to those will often be added Cimicifuga racemosa (Black cohosh), wild cherry, tartar emetic, and licorice. Other combinations will contain in addition to senega, white pine bark, wild cherry, squill, ipecac, Sanguinaria, opium, potassium nitrate, and methyl salicylate, tar, wild cherry, and yerba santa; squill, aconite, Grindelia, guaiac, ammonium carbonate, and bromides; ammonium chloride, squill, and opium; and in some tablet combinations with Hyoscyamus, licorice, tolu, cubeb, ipecac, and ammonium chloride.

Senega contains two saponins which are similar to those present in

Quillaja bark. Polygalic acid is precipitated by neutral lead acetate, and gives a ruby-red color with concentrated nitric acid, finally becoming yellow, and yellowish red; it gives a red to violet with concentrated sulphuric acid. It is slightly soluble in chloroform and from an acid solution is removed to a slight extent by that solvent. Senegin is the sapotoxin and is analogous to the Quillaja sapotoxin. It gives a yellow color with nitric acid.

Methyl salicylate is present in the drug and apparently increases with age. Preparations of which senega is a component will often indicate the drug by the presence of this ester.

Senega saponin, which consists probably of a mixture of polygalic acid and senegin, is used sparingly as a remedial agent.

Saponaria officinalis. Soapwort

While the root of this plant usually constitutes the drug, the entire herb is sometimes used in the form of a decoction. The root may be used as an alterative in the place of sarsaparilla. Its chief use is in venereal and cutaneous diseases, but it is also employed as a diuretic and diaphoretic.

The mixed glucosides resemble the crude saponin obtained from Quillaja. They produce sneezing and are soluble in water and hot alcohol, separating from the latter on cooling.

Rosenthaler and Strom [1] in reporting an investigation of Soapwort saponin assign the plant to the Gypsophilæ. As this genus is close to the Saponariæ and both are in the Caryophyllaceæ family the results of this research may be inserted at this point. On heating the saponin with 3 per cent sulphuric acid till a portion of the liquid gave no precipitate on further heating, the precipitated pro-sapogenin melted 207° on crystallizing from alcohol, and gave a semicarbazone, melting 241°. The pro-sapogenin when heated under pressure with 2 per cent sulphuric acid gave $C_{24}H_{34}O_5$, melting 267–268°, $(\alpha)_D = +90.86°$ in alcohol at 18° C. This substance was insoluble in water, but dissolved in organic solvents. Its semicarbazone melted 259–260°, and on oxidation with alkaline permanganate it yielded assymetric dimethylsuccinic acid, melting 130–131°.

The spikenard, Aralia racemosa, and wild sarsaparilla, Aralia nudicaulis, are two drug plants which may be mentioned in connection with this group, though their chemistry has never been the subject of research.

The rhizome of the spikenard furnishes the drug, and it is used as a gentle stimulant, diaphoretic, and alterative in chronic rheumatism, syphilis, and cutaneous affections. Certain well-known syrups and liquid mixtures contain the extract of spikenard with horehound, Sanguinaria, wild cherry, comfrey, and Inula helenium (elecampane); also

[1] Arch. Pharm., 1912, 250, 290.

with morphin, white pine bark, sassafras, wild cherry, Sanguinaria, and balsam poplar buds.

Aralia nudicaulis is a gentle stimulant and diaphoretic and is sometimes substituted for Sarsaparilla.

A closely related plant, Ginseng, Panax quinquifolium, furnishes a drug which though employed to a slight extent only in this country, is exported to China in enormous quantities. The wild plants have become so scarce and the demand for the drug so enormous that properly managed ginseng plantations are sources of great revenue to the owners. Ginseng seems to possess the alterative and diaphoretic characteristics of other saponin-containing drugs.

Caulophyllum thalictroides. Blue Cohosh

The root of the blue cohosh (Berberidaceæ) is a valuable uterine tonic drug and is used to a considerable extent in so-called " Female Remedies," where it is usually combined with Helonias, Viburnum opulus, V. prunifolium, Aletris, and Mitchella. These mixtures are prepared in the form of elixirs, cordials, wines, and tablets. A partially purified solid extract, is called caulophyllin. Emmenagogue compounds are composed of caulophyllin, ergot, savine, Polygonum punctatum (water pepper), and other drugs commonly used for the purpose.

Power and Salway [1] have made an exhaustive study of the drug and their results are summarized as follows:

An alcoholic extract of the ground material, when distilled in a current of steam, yielded a small amount of a pale yellow essential oil. From the alcoholic extract, the following definite compounds were isolated: (1) A crystalline alkaloid, $C_{12}H_{16}ON_2$ (m.p. 137°; $(\alpha)_D - 221.6°$), which has been identified as methylcytisin; the picrate melts at 228°. (2) A crystalline glucoside, caulosaponin, $C_{54}H_{88}O_{17}$, $4H_2O$ (m.p. 250–255°), which yields a deca-aceytl derivative, $C_{54}H_{78}O_{17}(CO \cdot CH_3)_{10}$, melting at 135–140° and on hydrolysis is resolved into caulosapogenin, $C_{42}H_{66}O_6$ (m.p. 315°), and dextrose. Caulosapogenin yields a tetra-acetyl derivative, $C_{42}H_{62}O_6(CO \cdot CH_3)_4$, melting at 120°, and a diacetyl derivative, $C_{42}H_{64}O_6(CO \cdot CH_3)_2$, melting at 160–162°, from which a crystalline monosodio-derivative, $C_{42}H_{63}O_6Na(CO \cdot CH_3)_2$, was prepared; it yielded, furthermore, a tetrabenzoyl derivative, $C_{42}H_{62}O_6(CO \cdot C_6H_5)_4$, melting at 288°, and a monomethyl ether, $C_{42}H_{65}O_5(O \cdot CH_3)$, which melts at 235°. (3) A new crystalline glucoside, caulophyllosaponin, $C_{66}H_{104}O_{17}$ (m.p. 250–260°; $(\alpha)_D + 32.3°$), which yields a deca-acetyl derivative, $C_{66}H_{94}O_{17}(CO \cdot CH_3)_{10}$, melting at 155–160°, and on hydrolysis is resolved into caulophyllosapogenin, $C_{56}H_{88}O_9$ (m.p. 315°) and arabinose. Caulophyllosapogenin yields

[1] Trans. Chem. Soc., Vol. 103, 1913, p. 191.

a hexa-acetyl derivative, $C_{56}H_{82}O_9(CO \cdot CH_3)_2$, melting at 160–162°, and a dimethyl ether, $C_{56}H_{86}O_7(O \cdot CH_3)_2$, which melts at 240–242°, and has $(\alpha)_D$+43.6°. (4) A phytosterol, $C_{27}H_{46}O$ (m.p. 153°). (5) Citrullol, $C_{28}H_{46}O_2(OH)_3$. (6) A mixture of fatty acids, consisting of palmitic, stearic, cerotic, oleic, and linolic acids. The alcoholic extract also contained a quantity of sugar, which yielded *d*-phenylglucosazone (m.p. 210°), and comparatively small amount of resinous material.

The above-mentioned methylcytisin, $C_{12}H_{16}ON_2$, represents the alkaloid previously obtained by J. U. Lloyd [1] and designated "caulophylline," but he did not succeed in crystallizing the base, and its composition was not determined.

The compound designated by the present authors as caulosaponin, $C_{54}H_{88}O_{17}$, $4H_2O$, is undoubtedly identical with a crystalline glucoside first obtained by J. U. Lloyd [2] and termed by him "Leontin," although the formula deduced from its analysis was not correct.

Chamælerium luteum. Starwort or False Unicorn

This plant, also known as Helonias, belongs to the Melanthaceæ and is one of our indigenous drugs. It is often confused with Aletris farinosa, the star grass or true unicorn root. The two drugs are often gathered and mistaken for each other by collectors. Helonias bullata is a closely allied plant and belongs to a monotypic genus.

The root possesses tonic and diuretic properties, and its extract is usually one of the constituents of the widely exploited remedies for troubles of the female reproductive organs. The Viburnum Compound type of preparations contain Chamælirium, Aletris, Viburnum opulus, and prunifolium, Mitchella repens (Squaw vine) and Caulophyllum thalictroides. Some of the mixtures will lack one or more of these drugs, but this is the general type. Tablets for leucorrhea, known as Helonias astringent, contain Chamælirium, Hyoscyamus, Opium, Hamamelis, tannic, salicylic and boric acids, alum, thymol, and eucalyptol.

The root contains a saponin-like substance which, when separated, forms a powder of the appearance of acacia, readily soluble in water and hot alcohol but not in other organic solvents. The other constituents of the drug have not been described.

Aletris farinosa. Star grass. True Unicorn-root

Aletris farinosa (Liliaceæ) may well be included at this point because of its confusion with the previous plant.

Aletris occurs in uterine tonics of the type mentioned under Chamælirium. The chemical constituents of the drug have never been studied.

[1] Proc. Amer. Pharm. Assoc., 1893, 41, 115.

[2] Drugs and Medicines of North America, Vol. II, 1887, p. 151.

Its recognition in medicinal mixtures can be accomplished with certainty only by examining microscopically the insoluble portions, and noting any characteristic tissues, which of course must be compared with slides obtained from authentic specimens of Aletris.

The presence of a saponin-containing drug is apparent by the frothing of the solution during the manipulation of the mixture while performing an analysis. If the preparation is a liquid, and an alcohol determination is in progress, the frothing and bubbling will often cause considerable inconvenience after the bulk of the alcohol has passed over, and may necessitate a redistillation of the distillate.

In the systematic scheme of analysis there will be more or less saponin dissolved out by the alcohol and subsequently taken up by water. The presence of the saponin will seriously interfere with the extractions of alkaloids and other principles by immiscible solvents because of the emulsion formed. This difficulty may be overcome either by shaking out with Prolius mixture or by adding basic lead acetate.

Most of the saponin-like substances, with the exception of small amounts of polygalic and quillaic acids, will be left in the aqueous solution after the extraction with immiscible solvents. If it is desired to separate these substances and subject them to characteristic tests, the above-mentioned solution, the original mixture, or an aqueous decoction obtained from the sample may be employed. The saponin is first extracted in a crude state and then purified. The solution is acidulated if alkaline, and then neutralized with magnesium carbonate and 20 grams or a proportionately less amount of ammonium sulphate are added and 10 mils of phenol (carbolic acid); after shaking, the phenol solution is separated and shaken with 50 mils of water and 100 mils of ether with the addition of alcohol if necessary to prevent emulsification; the aqueous layer is drawn off and allowed to dry in a desiccator. The residue is then washed with acetone or ether and after decanting the liquid, the residue is ready for testing. If dextrins are present they should be first removed by concentrating the solution to 20 mils and adding 100-120 mils of 95 per cent alcohol; after standing thirty minutes the mixture is boiled on the water-bath, filtered, the alcohol evaporated and the residue made up to 100 mils and treated as above.

Another procedure consists in treating the solution with lead subacetate and centrifuging, decomposing the precipitate with hydrogen sulphide in the presence of water, filtering, evaporating, extracting the residue with ether, and then dissolving the residue in water, filtering, and evaporating. Of course, if the aqueous solution contained sulphuric or other strong asids or their salts, the neutralized mixture must first be treated with barium chloride to remove them, otherwise their presence

would seriously interfere with the evaporation of the filtrate from the hydrogen sulphide treatment of the lead precipitate.

The saponin residue can then be subjected to identity tests. It should be divided into fractions by dissolving in water and evaporating 3 to 4 mils for the tests with concentrated sulphuric acid, nitric acid and Froehde's reagent. Portions of the aqueous solution may be treated with the salts of the heavy metals, gold and mercuric chlorides, ammoniacal silver nitrate, ferric chloride, permanganate and potassium ferricyanide, which are reduced, and with alkaline copper.

The hemolytic test is applied with a suspension of red-blood corpuscles prepared by washing sterile, defibrinated animal blood by centrifuging three times with physiological salt solution, and when the solution is clear removing 5 mils of the red corpulsces and diluting with 100 mils of the salt solution. A portion of the latter, well mixed, is treated with the saponin solution, which will cause hemolysis, recognized by the reddening of the solution due to the dissolved hemoglobin, and at the same time the cloudy suspension becomes clearer. A negative reaction does not necessarily mean the absence of a saponin-like body because the separation and purification of these bodies appears to change their physiological action, and furthermore it appears that those of the saponin class possess in the natural state the most pronounced action on the blood.

The aqueous solution may be further tested by adding hydrochloric acid to a strength of 2.5 per cent and then heating on the steam-bath until the solution ceases to foam. The pro-saponins thus formed are shaken out with ethyl acetate, the solvent washed free of acid, filtered through charcoal and evaporated. The residue should give an orange to cherry-red color with concentrated sulphuric acid, which on standing changes to violet; and its solution in dilute soda should foam on shaking.

No very reliable methods have as yet been evolved for estimating the saponins. The relations of the sapogenins to the sugars is not well understood, and any quantitative estimation would probably be based upon these products of hydrolysis. Korsakoff [1] describes a method for determining saponins in plants which might be made applicable to liquid medicines and to decoctions prepared from solids. The plant is completely dried, pulverized finely and treated with 60 per cent alcohol. After filtration, the alcohol is distilled off and the residue evaporated with calcined magnesia, the magnesia cake is pulverized, exhausted with boiling 80 per cent alcohol, filtered, and the filtrate precipitated with ether. The precipitate is dissolved in dilute sulphuric acid and hydrolyzed by heating for one hour in an autocalve to 100°. The liberated sapongenin is washed with water until neutral, dissolved in absolute alcohol, the solution evaporated to dryness and the sapogenin weighed. From the weight, the correspond-

[1] Comptes rend., 1912, 155, 844.

ing weight of the saponin can be calculated provided the analyst knows the proportion of sugar and sapogenin in the original saponin.

Carlifanti and Marzocchi [1] recommend the following method for determining saponin in emulsions: 100 mils of the emulsion are diluted with an equal volume of water and 400 mils of 95 per cent alcohol added gradually with agitation, the mixture being shaken frequently during two hours and allowed to stand twenty-four hours. The supernatant clear liquid is filtered through linen and the residual oil extracted with 60–65 per cent alcohol, and this extract also filtered and added to the first filtrate. The whole is neutralized with sodium carbonate and concentrated to 100 mils. A slight excess of phosphoric acid is added and saccharin and aromatic substances removed with ether. The residual aqueous liquid is treated with 20 grams of ammonium sulphate, and shaken out with several successive portions of 9 mils each of phenol. The phenol solution is shaken with a mixture of 100 mils of ether, 30 mils of water and 5 mils of alcohol and after twenty-four hours the aqueous solution is separated, evaporated on the water-bath, the residual saponin washed with acetone, dried, and weighed.

ARBUTIN

Arbutin is a glucoside which occurs in the leaves of a number of different species of plants. Certain evergreen plants whose leaves are official drugs contain arbutin and their medicinal value is probably dependent in part at least to its presence. Uva Ursi syn., Arctostaphylos Uva Ursi (Ericaceæ), bearberry or upland cranberry, and Chimaphila umbellata (Pyrolaceæ), pipsissewa or princess pine, are the two official drugs characterized by arbutin, and Kalmia latifolia (Ericaceæ), mountain laurel, non-official, also contains the glucoside. Arbutin is present in the leaves of other plants of the same families. It occurs in Vaccinium Vitis Idæa (Vacciniaceæ), mountain cranberry or whortleberry, an evergreen shrub whose leaves might be mistaken for the Uva Ursi.

UVA URSI

This drug is astringent and tonic, especially in those diseases affecting the urinary organs, hence it may be expected in remedies designed to alleviate gleet, nephritis, catarrh of the bladder, incontinence of urine, etc.

An extract of the drug is dispensed in popular form, and it is commonly combined with buchu, juniper berries, cubeb, and nitrous ether in the form of fluid extract buchu compound. It will be found in elixirs in the same combination, and with matico and Hydrangea. It is also present in some of the methylene-blue compounds, and potassium acetate or

[1] Boll. Chim. Farm., 1911, 50 , 609.

nitrate and Eupatorium may be added to the above-described combinations.

PIPSISSEWA—CHIMAPHILA UMBELLATA

Pipsissewa is an astringent, alterative, tonic, and diuretic drug, and is often substituted for Uva Ursi in remedies designed for the urinary tract. Its extract is used in chronic rheumatism and nephritis. It is combined with Stillingia in fluid extract stillingia compound, in which is also included Bikukulla canadensis, Iris, Sambucus, prickly ash berries, and coriander. Elixirs and syrups of this general composition will be encountered.

Chimaphila maculata, the spotted wintergreen, is an evergeren plant which grows in the same localities as the above and is often erroneously called pipsissewa.

KALMIA LATIFOLIA

The extract of mountain laurel has a limited use as an antisyphilitic and sedative. It is somewhat astringent and is employed in obstinate diarrhea.

ARBUTIN, $C_{12}H_{16}O_7$

Arbutin, to which the above drugs owe at least part of their therapeutic value, is also administered as a pure substance for diuretic purposes and as an urinary antiseptic.

Arbutin occurs in long, glistening, colorless needles, or as fine white crystalline, odorless powder having a bitter taste. It is soluble in 8 parts of water and 16 parts of alcohol, and somewhat soluble in ethyl acetate; very soluble in hot water and hot alcohol; insoluble in chloroform, ether, carbon disulphide. Its aqueous solution is neutral to litmus paper and is not precipitated by solutions of the metallic salts or by solutions of tannin. Its aqueous solution is colored blue by ferric chloride test solution, and when boiled with ferric chloride the pungent odor of quinone is evolved. By boiling with diluted sulphuric acid or by treatment with emulsin, arbutin is converted into glucose and hydroquinone.

When heated to 100° C. arbutin loses its water of hydration. At 195° C. the anhydrous glucoside melts.

Arbutin probably is accompanied by methyl arbutin in the plant. When it is hydrolyzed both the hydroquinone and glucose reduce Fehling's solution. Methyl hydroquinone does not reduce Fehling's solution, but it does give a blue color with ferric chloride while methyl arbutin does not.

Arbutin in aqueous solution gives a blue color when treated with a solution of 1 gram of sodium phosphomolybdate in 10 mils of concentrated

sulphuric acid and 20 mils water (Jungmann's reagent), followed by an equal volume of ammonia water. Methyl arbutin does not react with this reagent, but methyl hydroquinone does.

When arbutin is submitted to the action of emulsin, the liquid after the second day becomes pink and gradually darker until it is yellowish-brown. Under the same conditions a solution of methyl arbutin, if pure, will remain colorless for a long time.

If arbutin is treated in alcoholic solution with potassium hydroxide, a precipitate of the alkali with arbutin is obtained. The pure glucoside may be separated from this compound by filtering, washing with strong alcohol, boiling with glacial acetic acid under a reflux, neutralizing with calcium carbonate, distilling off any alcohol, and shaking out with ethyl acetate, from which on concentrating the arbutin will crystallize.

In the general scheme of analysis of medicinal products, arbutin will be left in solution after the mixture has been subjected to extraction with the different immiscible solvents. If the solution is concentrated, acidified with hydrochloric acid, and refluxed, the arbutin will be converted to hydroquinone and glucose, and the former may then be shaken out with ether and identified.

SALICIN AND BENZOYLSALICIN (POPULIN)

Salicin occurs in the bark of the white and black willow, Salix alba and S. nigra (Salicaceæ) and populin in the bark of some of the genus Populus, three representatives of which are used medicinally. Salix fragilis, crack willow, furnishes considerable of the salicin of commerce.

Salix alba is the European or white willow, a large tree, native of Europe, and introduced into this country. Its bark is used as a tonic, febrifuge, astringent, and antirheumatic, but has been largely superseded by its glucoside, salicin, which is now prepared in the pure condition and has the honor of being the only glucoside recognized in the U. S. Pharmacopœia.

Salix nigra, the black or swamp-willow, is native in this country and its bark possesses similar properties to that of S. alba. Its buds are also used medicinally and are claimed to exert a peculiar sedative influence on the sexual organs.

The barks of Populus alba, white or silver-leaf poplar, and P. tremuloides, quaking aspen, possess tonic, diuretic, and febrifugal properties. P. candicans, Balm of Gilead, is a large tree, the leaf buds and barks of which are used medicinally.

Salicin is marketed alone in the form of pills and tablets of different strengths from 1 to 5 grains. It is also combined in various mixtures with zinc oxide, belladonna, hydrastin, and pepsin; and with caffein, acetphenetidin, and ammonium salicylate.

Salicin, $C_{13}H_{18}O_7$, occurs as a crystalline silky powder or white, shining, tabular crystals or scales, melting 198–201°. It dissolves readily in hot water and hot alcohol, less readily in the cold, and is insoluble in the ordinary organic solvents. It is ortho-hydroxybenzyl glucoside, $C_6H_4(OC_6H_{11}O_5)CH_2OH$, and on hydrolysis by emulsion yields one molecule of saligenin (*o*-hydroxybenzyl alcohol) and one of glucose.

Salicin is not precipitated by lead acetate, basic lead acetate, tannin, or alkaloidal reagents. Its solution can therefore be clarified by lead, filtered, the lead removed by hydrogen sulphide, the solution neutralized and concentrated, and the glucoside recovered in part by crystallization provided it is present in fair amount.

The pure glucoside is neutral in reaction, lævorotatory $(\alpha)_D - 65°$ in aqueous solution. With concentrated sulphuric acid it gives a bright-red color which is destroyed by water with the deposition of a deep-red powder. When warmed with bichromate and sulphuric acid and then treated with water the odor of salicylic aldehyde is evolved. Froehde's reagent gives a purple color. Its aqueous solution is not colored by ferric chloride.

When boiled with dilute mineral acids salicin is hydrolyzed to dextrose and saliretin, the latter separating as a white substance, removable from acid solution by ether and capable of being converted to picric acid by nitric acid. If the hydrolysis is performed with emulsin at a temperature of 37° C., saligenin and dextrose are produced, and the former may be removed by shaking out with ether. It gives an indigo-blue color with ferric chloride and its other properties are fully described on page 553.

In the general scheme of analysis salicin will be left in the aqueous solution after the extraction with immiscible solvents, and its presence may be detected by the hydrolyzing of the solution with emulsin or by crystallizing as described above.

To estimate salicin in pills or tablets, a solution of the sample should be hydrolyzed by emulsin at 37° C. and the saligenin removed by ether, collected in a tared dish, the solvent evaporated and the residue weighed. If sugars are not present the dextrose could be determined and the salicin calculated, but most medicines usually contain some reducing sugar, which will of course vitiate any results obtained in this way.

SALINIGRIN, $C_{13}H_{16}O_7$

Salinigrin is reported by Jowett [1] as occurring in the bark of certain species of willow. It yields *m*-hydroxybenzaldehyde and glucose on hydrolysis. It melts at 195°, is fairly soluble in cold water, and very soluble on warming, sparingly soluble in cold alcohol, but more so in hot

[1] Trans. Chem. Soc., 1900, 707.

alcohol, sparingly soluble in hot acetone, almost insoluble in ether, petroleum ether, and chloroform. It gives no color reaction with sulphuric acid. It is lævorotatory $(\alpha)_{D16} = -87.3°$.

POPULIN, $C_{20}H_{22}O_8$

Populin or benzoylsalicin crystallizes with two molecules of water, which it loses at 100° C. The anhydrous substance melts 180°. It has a sweet taste, resembling that of licorice. It is slightly soluble in cold water and fairly soluble on boiling, slightly in alcohol and insoluble in ether. Sulphuric acid produces an amethyst-red color.

When boiled with barium hydroxide solution populin is converted to salicin and benzoic acid. Dilute mineral acids produce dextrose, benzoic acid, and saliretin. It is unacted upon by emulsin.

GLUCOSIDES OF THE BLACK HELLEBORE AND ALLIED DRUGS OF THE RANUNCULACEÆ

The rhizome of Helleborus niger (Ranunculaceæ), black hellebore or Christmas rose, is used principally in female pills and emmenagogues. It was formerly used for dropsy and epilepsy, and Bacher's pills for the former disorder were reputed to consist largely of this drug.

The types of female and emmenagogue pills containing black hellebore include in addition ergot or some proprietary preparation of ergot, aloes, ferrous sulphate, and oil or extract of savine; aloes, ferrous sulphate, Jamaica ginger, myrrh, soap, and Canella alba (cinnamon or whitewood bark), which represents the Hooper formula; cotton-root bark, ergot, ferrous sulphate, aloes, and savine oil.

The drug contains helleborin, $C_{36}H_{42}O_6$, a glucoside, forming white glistening needles, soluble in alcohol and ether, but insoluble in water. It is tasteless in the isolated condition, but in alcoholic solution it produces a burning, numbing sensation on the tongue. Concentrated sulphuric acid dissolves helleborin with an intense red coloration which gradually disappears and a white precipitate separates. It yields glucose and helleboresin on hydrolysis.

Helleborein, $C_{26}H_{44}O_{15}$, is found in the seeds and leaves of H. niger, but apparently is not present in the root. It forms fine, hygroscopic needles which are bitter and cause sneezing. It is soluble in water and alcohol, but not in ether, and hence can be easily separated from helleborin. With concentrated sulphuric acid a golden-yellow to reddish-brown coloration is obtained. It yields dextrose and helleboretin on hydrolysis, the latter being a violet blue substance when moist. Helleborein may be precipitated from aqueous solution by tannin, but not by basic lead acetate.

Glucosides of Adonis vernalis

Adonis vernalis (Ranunculaceæ), false hellebore or bird's eye, is a European and Asiatic species, the whole plant furnishing a drug having diuretic and heart-tonic properties. It is used for these purposes and also as a substitute for Helleborus niger.

It contains helleborein, adonidin, and picradonidin, all glucosides, and adonidic acid. Adonidin has been separated in a state of partial purity and appears to be an intensely bitter, odorless, hygroscopic substance, readily soluble in water and alcohol, but insoluble in chloroform and ether. It is not precipitated by either neutral or basic lead acetate, but is thrown out by tannin and is therefore readily separated from the adonidic acid which gives an insoluble compound with lead. When adonidin tannate is treated with zinc hydroxide and alcohol, evaporated to dryness at 40–50°, and extracted with absolute alcohol, the adonidin goes into solution.

Adonidin in its action closely resembles certain of the digitalis glucosides.

Adonis æstivalis, a closely allied plant of the same general habitat, probably contains adonidin. The drug is used as a remedy for obesity.

Actea spicata

The rhizome and rootlets of Actea spicata possess properties similar to Hellebore and are sometimes substituted for it. The plant is a native of Europe and Asia and is known as the baneberry or white cohosh.

In the United States we have two species of Actea having a limited use as drugs, A. alba and A. rubra. They are closely related to A. spicata, which is the type species and are known respectively as white cohosh or white baneberry and red cohosh, red baneberry or black cohosh (this term is misleading, as the true black cohosh is Cimicifuga racemosa).

The rhizomes of all these plants are violent purgatives, and according to Kraemer the European species contain helleborein.

Cimicifuga racemosa. Black Cohosh

The plant furnishing the drug so well known in this country as black cohosh or Macrotys is closely allied to the Acteæ, and the growing plant unless in blossom is readily mistaken for A. alba. Its reputation is dependent on its properties of relieving headache and uterine pains accompanying pregnancy, and in re-establishing the menstrual flow. It will consequently be found in remedies for female troubles. To a lesser extent black cohosh is used as a tonic, nervine, antispasmodic, and antirheumatic. As an antispasmodic it is employed in St. Vitus dance. It is dispensed alone and in combination in pills and tablets with wild cherry, ipecac, and licorice; with morphin and quinin in dysmenorrhea mixtures; with aloes,

cotton root bark, and ferrous sulphate; with Podophyllum resin, leptandra, juglans, and Capsicum; with aconite, belladonna, and colchicin; with lithium, salicylates, Phytolacca, and colchicin. In liquid mixtures it accompanies salicylic acid, potassium iodide, and Gelsemium. It is the essential ingredient of the so-called "Mothers' Cordials" or "Parturient Balms," and may be accompanied by aconite or Veratrum viride.

The root was used by the Indians as a remedy for snake bites, and the plant is also called black snakeroot.

The roots of C. Americana and C. cordifolia are undoubtedly often substituted for C. racemosa. The three plants grow in the Eastern floral section of the United States and the close resemblance of Americana to the common drug would be confusing to anyone but a trained drug collector or botanist.

The chemistry of the black cohosh rhizome is as yet unreported. It contains a resin, which is probably of complex composition. This resin is known as *macrotin* or *cimicifugin* and will be found listed in the drug catalogues under the head of "concentrations." It imparts a sweet taste to water, and upon prolonged chewing the taste becomes disagreeable and the throat experiences a burning or smarting sesnation. Tannin-like substances giving a black color with ferric chloride are present.

Extracts of fresh root are employed in eclectic practice. They have a sweet taste and a golden-yellow color.

CYANOGENETIC GLUCOSIDES, OIL OF BITTER ALMONDS AND HYDROGEN CYANIDE

Wild Cherry Bark and l-mandelonitrile Glucoside

Padus virginiana, syn. Prunus serotina (Amygdalaceæ) the wild black cherry, a large indigenous tree most abundant in the Southwestern States, furnishes the drug Prunus virginiana or wild-cherry bark. The tree sometimes attains a height of 90 feet with a maximum trunk diameter of 4 feet and is straight, the trunk being covered with a rough black bark, the young branches smooth and reddish. It is readily distinguished from Padus nana, the common choke cherry, a shrub growing from 2 to 10 feet, and from P. melanocarpa, the Rocky Mountain wild cherry, a smaller tree.

The bark is official in the U. S. Pharmacopœia and is collected in the autumn. The outside layer is first removed, so that the green layer underneath shows. The best grade is known as "thin green," the next grade "thick green," and the low grade "thick rossed."

Wild cherry bark is commonly employed as an ingredient of remedies intended for coughs and pulmonary complaints. It will be found in liquid White Pine compounds combined with white pine bark, balsam poplar buds, spikenard, Sanguinaria, Sassafras, morphin, and chloroform; in

sedative cough mixtures with codein, Cannabis sativa, white pine bark, Eriodictyon, balsam poplar buds, chloroform, and glycerin; with Eriodictyon, licorice, salicylic acid, Grindelia, pine tar and potassium bromide; with Sanguinaria, Marrubium, comfrey, spikenard, Inula, and Ceanothus americanus (Jersey tea). Alcoholic extracts of Wild cherry bark intended for the preparation of syrups and other purposes, often contain other drugs such as Marrubium (Horehound), Veratrum viride, Sanguinaria, and wild lettuce; or Cimicifuga, ipecac, licorice, and senega.

Elixirs intended as tonics and stimulants to the digestive tract will be found containing wild cherry, Taraxacum, and licorice; and gentian, Taraxacum, Eucalyptus, licorice, and Eriodictyon

The tablet and lozenge combinations are of the same general type as the liquids, thus we often meet with wild cherry combined with white pine bark, squill, senega, ipecac, Sanguinaria, opium, camphor, potassium nitrate, and methyl salicylate; with terpin hydrate, guaiac, opium, camphor, and belladonna; with licorice, pine tar, Eriodictyon, and senega; with licorice, colts foot, acacia, Marrubium, anise, cubeb. Capsicum, and tolu.

One of the most widely advertised preparations of wild cherry is the well-known confection recommended for coughs and colds. These wild cherry drops are sold in enormous quantities and consist almost entirely of sugar.

The characteristic glucoside of wild cherry bark is *l*-mandelonitrile glucoside, which also occurs in the bark of Cerasus padus syn., Prunus padus and isomeric with sambunigrin and prulauresin, the *β*-glucoside of dextro and racemic mandelonitrile respectively. Sambunigrin occurs in the leaves of Sambucus nigra, the common black elder and prulauresin in the leaves of the cherry-laurel, Prunus lauro-cerasus.

An aqueous decoction of the bark yields hydrogen cyanide and contains the cyanogenetic glucoside.

An alcoholic extract of the bark has been carefully examined by Power and Moore.[1] The portion of the alcoholic extract which was soluble in cold water contained the glucoside, sugar, tannin, benzoic, trimethyl gallic, and *p*-coumaric acids, and after heating with dilute sulphuric acid, *l*-mandelic acid and *β*-methylæsculetin. The alcoholic extract insoluble in cold water consisted of two resinous substances, one a greenish body insoluble in warm water and the other a brown amorphous product soluble in hot water and depositing slowly on standing. The green resin, amounting to about 1 per cent of the weight of the bark, yielded a phytosterol, $C_{27}H_{46}O$, melting 135–136°, $(\alpha)_D - 34.0°$; palmitic, stearic, oleic, linolic acids, and apparently a very little isolinolenic acid, ipuranol; and after acid hydrolysis oleic acid, dextrose, and *β*-methylæsculetin, $C_{10}H_8O_4$, melting 204°. The

[1] Trans. Chem. Soc., 1909, 243.

brown resin, amounting to about 1 per cent of the weight of the bark, yielded after acid hydrolysis, a trace of a phytosterol, small amounts of oleic acid, β-methylæsculetin, dextrose, insoluble red resinous material, which on fusion with potassium hydroxide gave formic, acetic, butyric, and proto-catechuic acids.

An alcoholic extract of the bark, when distilled with steam, yielded small amounts of benzoic acid and an essential oil, but no hydrocyanic acid. The bark contains an enzyme which hydrolyzes β-glucosides.

The separation of the *l*-mandelonitrile glucoside in a condition of purity is attended with some difficulty and the following method was adopted by Power and Moore in recovering it from the drug:

One kilogram of the original alcoholic extract, representing about 3.8 kilograms of the bark, was mixed with 2 liters of water, and the volatile constituents were removed by distillation with steam. The contents of the distillation flask were then filtered while hot from the previously described green resin, the latter being thoroughly washed with water, and the washings added to the filtrate. After allowing the combined aqueous filtrate and washings to stand for several weeks, a quantity of the previously described brown resin was deposited, from which the clear liquid was decanted. This liquid, being large in amount, was divided into four portions, each of which was concentrated as far as possible under diminished pressure. To each portion 200 mils of alcohol were then added, and, after complete solution, the thin syrups were again concentrated under diminished pressure, this operation being repeated until the mass became too viscid for further concentration. Each portion was then dissolved in 200 mils of absolute alcohol, and to the thin syrups so obtained 1 liter of boiling, dry ethyl acetate was added in each case. After standing for several hours, the liquids were decanted from the precipitated syrup, concentrated to about 100 mils, and while still hot, 500 mils of boiling, dry ethylacetate added to each portion. They were again allowed to stand for several hours, when some syrupy material was deposited, from which the clear ethyl acetate liquids were decanted. These were then united, concentrated to the measure of 500 mils, and, after cooling, 500 mils of dry ether added. The clear liquid was then separated, the solvent completely removed, and the residue dissolved in about 300 mils of cold water. This aqueous liquid was shaken with small successive portions of ether in order to remove the acids which were known to be present, after which it was treated with a solution of normal lead acetate until no further precipitate was produced. The yellow precipitate was removed by filtration with the aid of the pump, and the aqueous filtrate concentrated on the water-bath under diminished pressure to about 30–40 mils. A mixture of 300 mils of alcohol and 300 mils of ethyl acetate was then added, and the whole allowed to stand overnight. The clear liquid,

decanted from a small amount of a yellow precipitate, was concentrated to a small volume, the residual product being then dissolved in water and treated with hydrogen sulphide for the removal of the lead. After filtration, the aqueous liquid was concentrated under diminished pressure to the measure of about 50 mils, when an excess of calcium carbonate was added to neutralize the free acetic acid, and the mass then extracted with alcohol. This alcoholic extract was evaporated to dryness on a water-bath under diminished pressure, and the residue dissolved in ethyl acetate, when, after concentrating the solution to about 20 mils, the glucoside slowly crystallized in small, colorless needles. It was recrystallized from ethyl acetate, when two crops of crystals were obtained. The first fraction of crystals, which amounted to 0.6 gram, melted initially at 144–146°, and, after further crystallization, at 145–147°. The second fraction of crystals, which was very small in amount (about 0.1 gram), was somewhat less pure, and melted at 135–140°. Both these fractions, when treated with emulsin, yielded hydrogen cyanide, benzaldehyde, and glucose. The first fraction was analyzed, with the following result:

0.1392 gave 0.2904 CO_2 and 0.0750 H_2O. C = 56.9; H = 6.0. $C_{14}H_{17}O_6N$ requires C = 56.9 H = 5.8 per cent.

0.3605, dissolved in 20 mils of water, gave in a 2 dcm. tube $\alpha_D - 1°4'$, whence $(\alpha)_D - 29.6°$.

The above described cyanogenetic compound was thus identified as *l*-mandelonitrile glucoside.

A determination of the specific rotatory power of the small fraction of glucoside melting at 135–140° gave the following result:

0.0956, dissolved in 20 mils of water, gave in a 2-dcm. tube $\alpha_D - 0°14'$, whence $(\alpha)_D - 24.4°$.

It has the composition $C_6H_5CH(OH)CN \cdot C_6H_{10}O_5$, and when pure melts 147°, $(\alpha)_D - 26°$ or $-29.6°$, hydrolyzing to dextrose and *d*-mandelonitrile, $C_6H_5CH(OH)CN$. When treated with emulsin it yields hydrogen cyanide, benzaldehyde, and glucose.

The isolation of β-methylæsculetin would indicate that the bark contained a small quantity of the glucoside methylæsculin.

Amygdalin, $C_{20}H_{27}O_{11}N$, melts 200° and when treated with emulsin yields hydrogen cyanide, benzaldehyde, and two molecules of dextrose.

Sambunigrin and prulauresin, isomeric with *l*-mandelonitrile glucoside, melt and have specific rotation respectively 151° $(\alpha)_D - 76°$ and 122° $(\alpha)_D - 52.75°$. The former hydrolyses to dextrose and *l*-mandelonitrile and the latter to dextrose and *d*-*l*-mandelonitrile.

The detection of wild-cherry bark in medicinal preparations is usually accomplished by setting free and isolating the hydrogen cyanide and by noting the fluorescence of an extract of the sample due to the methyl æsculin. These tests are not conclusive, but at present they take us as far as we can go. It is not possible to isolate the characteristic glucoside from the amount of material which the analyst ordinarily has at his disposal.

The hydrogen cyanide can be isolated both qualitatively and quantitatively by exhausting the sample with hot alcohol, removing the solvent by evaporation over the steam-bath, transferring the residue with 50 mils water to a distilling flask fitted for steam distillation, adding 10 mils of dilute hydrochloric or sulphuric acid and distilling, keeping the water volume fairly constant until the distillate gives no further test for hydrogen cyanide. To determine the quantity of this substance the distillate should be treated with an excess of sodium bicarbonate and then titrated with iodine to the appearance of a yellow color.

Cherry-laurel Water

Cherry-laurel water is prepared by aqueous distillation of the fresh leaves of Prunus lauro-cerasus. The finished product is often employed in Europe as a sedative narcotic but has never been used to any extent as a drug in this country. The distillate contains the essential oil of the leaf, benzaldehyde, and hydrogen cyanide, but the two latter gradually establish an equilibrium, and the liquid then contains hydrogen cyanide and benzaldehyde cyanohydrin.

$$HCN + C_6H_5CHO \longleftrightarrow C_6H_5CH(OH)\cdot CN$$

The rapidity with which the final condition of equilibrium is attained depends on whether the solution is more or less acid.

The product is an unsatisfactory preparation at best and the cyanogenetic substances are variable. If assayed according to the official method for hydrocyanic acid, the determination should be made as soon as the product is distilled, otherwise the results will not show the total quantity of cyanide bodies present.

A distillate from bitter almonds, known as bitter almond water, is prepared in the same way as cherry-laurel water and consists of the same or closely related ingredients. It has been largely replaced by benzaldehyde water.

Power and Moore [1] examined the leaves of Padus virginiana and found present *l*-mandelonitrile glucoside, the same substance present in the bark,

[1] Trans. Chem. Soc., 1910, 97, 1099.

and also an enzyme which hydrolyzes β-glucosides. It is not unlikely that these or similar substances, possibly the racemic form of the glucosides, are present in the leaves of Prunus lauro-cerasus and give rise to the products of hydrolysis found in the distillate.

Hydrocyanic Acid, HCN

Hydrocyanic acid is used in medicine for alleviating spasmodic conditions, nervous coughing, whooping cough, vomiting, colic, angina pectoris and cholera. Locally it is applied to the unbroken skin to allay itching. It is, of course, used in very weak solutions and the pharmacopœial acid is of 2 per cent strength. It is one of the constituents of chlorodyne and other mixtures of this type, being combined with morphin, Cannabis indica, and chloroform.

It is of still further interest to the drug chemist as it occurs as benzaldehyde cyanhydrin in a number of pharmaceutical preparations which are made from vegetable products containing amygdalin, and possibly other glucosides of similar nature. Thus it is a constant component of Cherry-laurel water or Kirschwasser, an anodyne and antispasmodic remedy distilled from the leaves of the cherry laurel (Prunus laurocerasus), and in natural oil of bitter almonds, and in bitter almond water.

The pure acid is a clear colorless liquid with an unmistakable odor, boiling 26.5° and solidifying at −15°. It is soluble in water, alcohol, and ether. Its vapor burns in the air with a violet-blue flame, forming carbon dioxide, nitrogen, and water. It is a weak acid and only temporarily reddens litmus. It is known practically only in dilute solutions which are very poisonous.

Hydrogen peroxide changes it to oxamide. Silver nitrate produces a voluminous precipitate which is insoluble in dilute nitric acid but will dissolve in concentrated acid. Silver cyanide when boiled with hydrochloric acid reacts and the odor of hydrocyanic acid is apparent.

Hydrocyanic acid may be detected in dilute solutions by adding a few drops of potassium nitrite solution followed by a few drops of ferrous sulphate and enough dilute sulphuric acid to cause the yellow-brown color of the basic ferric salt to become yellow. The liquid is then boiled, cooled, the excess of iron precipitated with ammonia and filtered. A few drops of freshly prepared ammonium sulphide are then added and a violet color will appear, changing through blue and green to a yellow color.

An alkaline solution of hydrocyanic acid or a cyanide on treatment with ferrous sulphate and hydrogen peroxide, followed by an excess of hydrochloric acid will give a precipitate of Prussian blue.

Hydrocyanic acid can be estimated in dilute solution or in the almond and cherry waters by weighing out a sample, adding a slight excess of

magnesium oxide and a few drops of potassium chromate and then titrating with silver nitrate until a brownish-red color is obtained.

$$1 \text{ mil } N/10\ AgNO_3 = .002702 \text{ gm. } HCN$$

The cyanides of mercury and potassium are used to some extent medicinally. The former often replaces mercuric chloride as an antiseptic, and the latter is a sedative and anodyne.

Hydrogen peroxide is one of the accredited antidotes in cases of cyanide poisoning, hence it should be looked for in any mixture advertised for this purpose.

Oil of Bitter Almond

Oil of bitter almond is obtained by macerating the kernels of Prunus amygdalus or of Prunus armenicaca (apricot) with water and distilling. The commercial oil contains a small quantity of hydrogen cyanide and cyanogenetic products (benzaldehyde-cyanhydrin). When freshly distilled it is a colorless liquid, but as it ages it becomes yellow. Its use in medicine is limited. It may be expected in nerve sedatives and cough remedies and to allay severe itching. It is also used as a flavoring agent and to conceal the taste of cod liver and castor oils. For all practical purposes the artificial benzaldehyde answers all the requirements of the distilled oil and when pure is much less poisonous.

In order to test for hydrogen cyanide 10–15 drops of the oil are shaken with 2–3 drops of a strong solution of sodium hydroxide. Several drops of ferrous sulphate containing some ferric salt or a little hydrogen peroxide are added and the mixture shaken and acidulated with hydrochloric acid. Upon solution of the iron salts a precipitate of Prussian blue results if hydrogen cyanide is present.

Nitrobenzol is sometimes used as an adulterant and may be detected by dissolving the oil in twenty times its volume of alcohol, adding water until turbidity results, and then introducing zinc and sulphuric acid to generate a slow stream of hydrogen. After several hours the solution is filtered, the alcohol evaporated, and the residual solution boiled with a drop of potassium bichromate which will cause the development of a violet color.

The presence of non-aldehydic constituents may be detected by shaking 5 grams of the sample with 45 grams of saturated sodium bisulphite solution and then adding water and warming, whereupon non-aldehydic substances will rise to the surface.

Artificial benzaldehyde is considered an adulterant of this oil and its presence was formerly considered as established if chlorine could be detected. There are many reasons why this is a very doubtful criterion as to the presence of artificial benzaldehyde, and at the present time an

analyst should draw no definite conclusions on the subject unless he has more substantial proof of the sophistication.

Probably the simplest method of detecting the presence of chlorine products would be to boil the suspected sample under a reflux with alcoholic potash, evaporate the alcohol, take up with water and remove the oily constituents with ether, precipitate the aqueous liquid with silver nitrate in presence of nitric acid, and identify the silver precipitate as the chloride in the presence of cyanide.

Free hydrogen cyanide is determined according to the method described under hydrogen cyanide. Applied to the oil, 1 gram of the sample is carefully weighed into a small Erlenmeyer flask, and 10 mils of a mixture of freshly prepared magnesium hydroxide and several drops of potassium chromate added. The mixture is then titrated with N/10 silver nitrate until the formation of red silver chromate.

The total cyanogenetic constituents are determined by saponifying a weighed sample with alcoholic potash, diluting with water, filtering if necessary, and precipitating with silver nitrate in the presence of nitric acid. After the liquid has become clear the silver cyanide is collected on a tared Gooch, washed with water and dried at 100°. The silver precipitate obtained in this way represents all of the hydrogen cyanide, free and combined, and with the figures of both determinations the relative amounts of each are a simple matter of calculation.

GLUCOSIDES OF THE MUSTARD SEED

Sinalbin, $C_{30}H_{42}O_{15}N_2S_2 \cdot 5H_2O$.

Sinigrin, $C_{10}H_{16}O_9NS_2K$

Mustard seed is the ripe seed of Sinapis alba L. (White mustard), (Cruciferæ), Brassica niger L. (Black mustard), Brassica junicea, or the varieties or closely related species of the type of B. nigra and B. junicea.

Sinalbin occurs in the white mustard seed and sinigrin in the black. In addition to these glucosides, sinapin, $C_{16}H_{23}O_5N$, an alkaloid, occurs in both varieties of seeds. Another important constituent is an enzyme, myrosin, which readily hydrolyzes the glucosides when the seeds are powdered and digested with water at the ordinary temperature.

Black mustard seed deprived of its fixed oil is used in the manufacture of mustard plasters. As a household remedy, commercial ground mustard, which is usually prepared from both white and black seeds, is used in poultices, as an emetic and for relieving obstinate hiccough.

Sinalbin

Sinalbin forms yellowish needles, melting anhydrous at 138–140°, slightly soluble in cold water and alcohol, readily in hot water and insol-

uble in ether. Its aqueous solution is alkaline, bitter, and gives a yellow color with alkalies.

On hydrolysis by myrosin, it yields dextrose, sinalbin, mustard oil (*p*-hydroxybenzylisothiocyanate), and sinapin hydrogen sulphate.

$$C_{30}H_{42}O_{15}N_2S_2 + H_2O = C_6H_{12}O_6 + C_7H_7O \cdot NCS + C_{16}H_{24}O_5N \cdot H_2SO_4$$

Sinigrin

Sinigrin is potassium myronate. It crystallizes in colorless needles, melting 126–130°, soluble in water, somewhat soluble in warm methyl alcohol, sparingly in cold alcohol, insoluble in ether, chloroform, and acetone. It is converted by myrosin to dextrose, allyl isothiocyanate, and potassium bisulphate.

$$C_{10}H_{16}O_9NS_2K + H_2O = C_6H_{12}O_6 + C_3H_5NCS + KHSO_4$$

Allyl isothiocyanate is commonly known as mustard oil, and is a volatile liquid with a pungent odor and taste. The sinalbin mustard oil is not volatile.

Sinigrin gives a white precipitate with basic lead acetate in presence of ammonia.

Sinapin

Sinapin is not known in the free state, as it decomposes into cholin and sinapic acid when solutions containing it are evaporated. It exists as the thiocyanate in the seeds and is one of the products of hydrolysis of sinalbin. Aqueous solutions of the free base are alkaline and have a yellow color.

Sinapin may be separated from the thiocyanate by treating the solution with silver sulphate, separating the silver precipitate, removing the sulphate with barium hydroxide, leaving the free alkaloid.

Sinapic acid, $C_{11}H_{12}O_5$, one of its products of decomposition, crystallizes from alcohol in prisms, melting 191–192°.

The percentage of allyl isocyanate in mustard seed is ascertained by the method described on page 51.

Bitter Tonic Drugs

GENTIOPICRIN AND THE GENTIAN GLUCOSIDES

Gentiopicrin occurs in the root and other parts of the anatomy of several of the Gentianaceæ. The rhizome and roots of Gentiana lutea furnish the official drug, gentian, which has attained wide popularity as a bitter tonic and which enters into the composition of a variety of for-

mulas. The plant grows among the Apennines, the Alps, the Pyrenees, and in other mountainous or elevated regions of Europe. Several of the species are credited with analogous medicinal properties, and their roots are either mixed with the official drug or are used locally for the same purposes. G. lutea requires several years to reach maturity, but the root is gathered at any period during the growth of the plant.

The rhizome and roots of G. elliotii, syn., Dasystephana parvifolia, indigenous to the southeastern part of this country, were at one time official.

Liquid extracts of gentian are usually flavored with bitter orange peel, cardamon, or lemon peel. Of the numerous types of pill and tablet formulas containing extract of gentian may be mentioned those in which it is combined with Podophyllum, colocynth, Hyoscyamus, Cascara sagrada, Juglans, Nux Vomica and Apocynum; with strychnin, ipecac, black pepper, and oil of cloves; with quinidin, cinchonidin, Althea, and hydrochloric acid (Catarrh formula); with colocynth, jalap, Podophyllum, leptandra, Hyoscyamus and oil of peppermint (cathartic compound); with cinchonidin, cardamom, pimento, ginger, pepsin, and hydrochloric acid; with aloes, rhubarb, and caraway; with ipecac, opium, mercury, and chalk; with quinin, arsenic, and atropin; with strychnin, ipecac, Capsicum, rhubarb, and sodium bicarbonate; with Nux Vomica, Ignatia, Cinchona, Calumba, German chamomile, phosphorus, and aromatic powder; with quinin, strychnin, arsenous acid, and reduced iron; with quassia; in Warburg's tincture, which is dispensed in the liquid, capsule, pill, and tablet form, where it occurs with rhubarb, angelica seed, Inula, saffron, fennel, zedoary, cubeb, myrrh, white agaric, camphor, quinin, or cinchonin and cinchonidin, with and without aloes.

Elixirs of gentian alone and with other well-known bitters such as colocynth and quassia, will often be encountered, as well as more complex mixtures containing Taraxacum, Yerba Santa, licorice, wild cherry, and Eucalyptus; with iron citrochloride or pyrophosphate with or without pepsin.

Adulteration with Rumex alpinus has been reported. The root of Frasera carolinensis, American calomba or yellow gentian, which grows in the Eastern United States and Canada, resembles in the whole condition the official gentian, but is lighter in color. It contains gentiopicrin.

The fresh root contains the glucosides, gentiopicrin, and gentiamarin, and possibly a third known as gentiin, and a carefully prepared dialyzed extract of the fresh root in 60 per cent alcohol contains them in an unaltered condition. As the root is ordinarily dried for the market these glucosides are broken down, due to the action of emulsin, and as they are also hydrolyzed even in the presence of alcohol, ordinary medicinal preparations contain only their decomposition products. This action seems to impair

but little the bitter effect of the drug, and the therapeutic significance of the undecomposed glucosides has not yet been determined, though their decomposition is detrimental to the identification of the drug by chemical means.

The glucosides are not precipitated by lead subacetate, and they may be separated from the root or a drug extract by extracting with alcohol.

If carefully dried under cover, gentian will lose but a small quantity of gentiopicrin, and the marketable drug may then contain from 5–6 per cent, the loss ordinarily sustained is due to fermentation previous to or during drying. Tinctures made by macerating for a long period with 60 per cent alcohol lose practically all the gentiopicrin, but if the powdered root is heated to boiling with 60 per cent alcohol for twenty minutes and then cooled and macerated, the tincture will contain the glucosides.

The fresh gentian root contains the glucosides above mentioned, gentisin, quercitrin or an allied product, saccharose and possibly other sugars, pectin and other substances not yet studied. Unless carefully dried the saccharose is changed during the process of curing.

Gentiopicrin

Gentiopicrin crystallizes in two forms, anhydrous, $C_{10}H_{20}O_9$, and hydrated, $C_{10}H_{20}O_9+\frac{1}{2}H_2O$; the former, melting 191°, is obtained from absolute alcohol or anhydrous ethyl acetate; the latter, melting 122°, from water or hydrated ethyl acetate, it is dehydrated at 105°. It has a lactone structure and forms gentiopicrinates with alkalies. Hydrated gentiopicrin has $(\alpha)_D-198.75$. It forms a pentacetyl derivative, melting 139°. It is slightly soluble in ether and is removed from acid solutions to a slight extent by that solvent. On hydrolysis by emulsin or dilute sulphuric acid it yields gentiogenin, which is insoluble in 60 per cent alcohol.

Gentiogenin gives a characteristic reaction with concentrated sulphuric acid. If dissolved in 3–4 mils of 95 per cent alcohol and an equal volume of acid added without mixing, a blue zone appears at the point of contact. If dissolved in the acid the solution is brown, and adding water drop by drop the blue color develops.

Gentiamarin, $C_{16}H_{20}O_{10}$ or $C_{16}H_{22}O_{10}$

Gentiamarin is amorphous and bitter, $(\alpha)_D-80°$ or $-90°$, the higher value being due to traces of gentiopicrin. When hydrolyzed with sulphuric acid it gives an amorphous brown substance which is not gentiogenin, as it does not give a blue color with sulphuric acid. It does not possess a lactone structure nor does it combine with alkalies nor yield an acetyl derivative.

Gentiin

Gentiin crystallizes from 60 per cent alcohol in pale yellow microscopic needles, melting 274°; slightly soluble in water and gives a blackish-green color with ferric chloride. It has no lactone structure. With nitric acid a green solution is obtained, changing to orange on the addition of alkali. When hydrolyzed in a sealed tube with dilute sulphuric acid, glucose and xylose are formed, together with a yellow, crystalline substance, $C_{14}H_{10}O_5$, melting 225°, and subliming 195°.

The identification of extract of gentian root in medicines, unless present in large quantity, is not easy of accomplishment because of the instability of the active principles. The separation and identification of gentiopicrin and gentiamarin may be accomplished by following Tanret's procedure which is also a quantitative method for a proximate assay of the root. The details are as follows:

An alcoholic extract of the drug or of a medicinal mixture is freed of its alcohol and dissolved in water. It is then extracted several times with ethyl acetate saturated with water, the combined solvents filtered, concentrated, and allowed to stand, when a syrupy deposit will be obtained. This deposit contains the gentiopicrin and gentiamarin with a little gentiin, the greater portion of the latter remaining behind in the ethyl acetate.

The syrupy mixture is then dissolved in an equal weight of boiling absolute alcohol, and on cooling impure gentiopicrin will crystallize. By repeated crystallization from ethyl acetate containing 2 per cent water, the more soluble gentiin will be eliminated and pure gentiopicrin obtained. The alcoholic mother liquor from which the impure gentiopicrin first crystallized is evaporated to a syrup, extracted with ether and chloroform, then dissolved in water, and precipitated with a 20 per cent solution of tannin. After filtering, the solution is treated with a large excess of tannin and the glucosidal tannate salted out in the cold with magnesium sulphate, and then extracted with 80 per cent alcohol. The alcoholic solution is shaken with hydrated lead oxide, filtered, the excess of lead removed and the filtered alcoholic solution concentrated *in vacuo*, the residue consisting of gentiamarin.

The gentiin remaining in the ethyl acetate is recovered by evaporating the solvent and crystallizing the glucoside from 60 per cent alcohol.

Chirata

Swertia chirata (Gentianaceæ) is a simple bitter tonic having a limited medicinal use. The entire herb constitutes the drug.

Chirata is sometimes combined with iron, Euonymus, Podophyllum resin, Veronica, and creosote.

The chemistry of this drug has been imperfectly determined, but it

contains one or more bitter principles which are probably related to those occurring in other drugs of the Gentianaceæ. The presence of ophelic acid, $C_{13}H_{20}O_{10}$, and chiratin have been reported. The latter is described as a yellow hygroscopic powder, sparingly soluble in cold water, but readily in hot water, alcohol, and ether, with a neutral reaction, and giving a heavy precipitate with tannic acid. On hydrolysis it yields ophelic acid and a bitter substance.

Chirata is a native of India, where its medicinal virtues have been held in high repute for a long time. The name has been applied to many other bitter drugs sold in India and some of these false chiratas have reached our markets.

Elaterium and Elaterin

The juice of the fruit of Ecballium elaterium (Cucurbitaceæ) yields a sediment to which the name elaterium has been given. This product, which has powerful purgative properties, contains about 30 per cent of commercial elaterin, which is resolvable into two isomeric principles, α- and β-elaterin. α-elaterin constitutes from 60–80 per cent of commercial elaterin and is devoid of purgative action, the physiological property of the drug being due to the β-compound. Elaterin occurs as such in the fresh juice and is not in glucosidic combination.

Both elaterium and commercial elaterin are employed as medicinal agents and are dispensed chiefly in the form of pills and tablets of small grainage. On account of their powerful action neither the drug nor its active principle are sold as popular remedies, but are prescribed in the treatment of dropsy.

The crude drug varies greatly in its strength, due to amount of elaterin present. It occurs in light, friable, flat, or slightly curved opaque cakes about $\frac{1}{10}$ in. thick, of a greenish-gray color, becoming yellowish by exposure, with a faint tea-like odor, and a bitter, somewhat acrid taste. It is inflammable and so light that it swims when thrown upon water. Inferior specimens are paler in color without any green tint, soft and friable, and usually sink in water. The best grades come from England, where the plant is cultivated and the elaterium prepared as a regular industry. About 6 per cent of the drug is soluble in water. A small quantity of starch is present in authentic specimens.

Alcohol and chloroform extract a dark-green resin. The resin dissolves freely in ether and may be thus readily separated from the elaterin, which is only sparingly soluble. The elaterin of the pharmacopœias is a nearly colorless, tasteless, crystalline powder, melting and decomposing at 217–220°, sparingly soluble in ether and alcohol, readily in chloroform, and precipitated from its solution in the latter by the addition of ether.

Elaterin is soluble in alkalies and is precipitated by acids. It may

be removed from acid aqueous mixtures by ether, but more readily by chloroform.

Elaterin and elaterin residues give with concentrated sulphuric acid, a pink color, quickly changing to reddish-yellow; with Froehde's reagent a pink to yellowish-green to deep green; with ammonium vanadate in sulphuric acid, an intense blue, soon fading to dirty yellow, undissolved crystals becoming orange and finally deep green, which is a very characteristic reaction.

Power and Moore [1] by fractionally crystallizing commercial elaterin from absolute alcohol, have separated two isomeric substances to which they give the names α- and β-elaterin.

α-elaterin, $C_{28}H_{38}O_7$, forms hexagonal prisms, melting 230° C., very sparingly soluble in absolute alcohol, $(\alpha)_D - 52.9°$ in chloroform. The molecule contains an acetyl, a lactone, and two phenolic groups. When oxidized with chromic acid it yields a ketone elaterone, $C_{24}H_{30}O_5$, crystallizing from alcohol in needles, melting 300°, $(\alpha)_D + 120.5°$ in chloroform.

β-elaterin has apparently the same empirical composition and crystallizes in plates which are readily soluble in absolute alcohol. It melts 190–195°, $(\alpha)_D + 13.9°$. It is to this body that the purgative value of elaterin and the drug is due.

Power and Moore conclude that the only means of arriving at the physiological value of the drug would be to adopt definite limits for its specific optical rotation. The dosage of a product conforming to such a standard could then be adjusted in accordance with the results obtained by physiological or chemical tests.

Colocynth

The pulp of the dried, peeled fruit of Citrullus colocynthus (Cucurbitaceæ) is the official drug colocynth. It is a powerful hepatic stimulant and hydragogue cathartic and has an extended use in medicine, being usually combined with other cathartics and dispensed in the form of pills and tablets. The well-known colocynth comp. pills consist of colocynth, aloes, scammony, and oil of cloves, and when made according to the British formula contain potassium sulphate in addition. The U. S. P. vegetable cathartic pills consist of colocynth comp., Hyoscyamus, jalap, leptandra, Podophyllum, and oil of peppermint. Colocynth comp. is present in several types of mixtures with Hyoscyamus, e.g., with Hyoscyamus and mercury mass, with podophyllum, with calomel and gentian, with rhubarb and oil caraway, with aloes and tartar emetic, with Nux Vomica, with jalap, Podophyllum and capsicum; with calomel and Podo-

[1] Pharm. J., 1909.

phyllum; and with calomel and Colchicum. Formulas similar to the U. S. P. cathartic compound also may contain gentian, gamboge, soap, cardamon, ginger, rhubarb, leptandra, and ipecac. Colocynth compound occurs with Cinchona alkaloids, oleoresin pepper and ferrous sulphate; strychnin, belladonna, ipecac, and mercury mass; rhubarb, aloes and mercury mass; with calomel; with mercury mass alone, and with ipecac; with Podophyllum; with Podophyllum and calomel; with Podophyllum, calomel, belladonna, ipecac, Nux Vomica, and oil of anise; with Podophyllum, aloin, Nux Vomica, Capsicum, and croton oil; with inspissated ox gall, pancreatin, quinin, Nux Vomica, and Taraxacum; with quinin. Colchicum, Hyoscyamus, opium, and mercury mass.

Powdered colocynth or its extract is combined with aloes, gamboge, soap, and anise; with Podophyllum, Hyoscyamus, Cascara sagrada, juglans, Nux vomica, gentian, and Apocynum cannabinum, and in other formulas of the same general character as those above described, but in most products colocynth is added as the extract of colocynth comp., and if the formula is given, the grainage is usually expressed in terms of the latter compound and not as colocynth extract alone.

The presence of seeds in the powdered drug is indicated by the appearance of numerous albuminous granules derived from the cotyledons. If the powder is placed on a glass slide, with a drop of water and a cover glass rubbed over it, fragments of the double-walled embryo sac show on the outer side elongated, more or less hexagonal, thin-walled cells, and on the inner side irregular, tabular, thick-walled cells. An amount of fixed oil in excess of 2 per cent, determined by petroleum ether extraction is further indication of the presence of seeds. The ash of colocynth pulp may run from 7.2–13.5 per cent.

Power and Moore [1] found that the active principles of colocynth are a weak alkaloid and a non-basic indeterminate substance in the resin. The alkaloid has an extremely bitter taste, is soluble in water and dilute acids and precipitated by the ordinary alkaloidal reagents, tannin and basic lead acetate. It is soluble in chloroform, but not to any extent in ether. It is removed from its chloroformic solution by hydrochloric acid. The resin is only partly soluble in alcohol, the insoluble portion containing α-elaterin, melting 232°, sparingly soluble in ether, and less so in alcohol and water, but readily in chloroform. The alcoholic soluble portions contain non-glucosidic substances of a purgative nature.

Power and Moore also isolated from the pulp a new phytosterol glucoside to which the name citrullol was given. This substance is soluble in water, from which it may be removed by repeated extraction with ether. On crystallization from pyridin it melts 285–290°. When dissolved in chloroform with a little acetic anhydride, the addition of concentrated

[1] Trans. Chem. Soc., 1910, 99.

sulphuric acid will produce a series of color reactions similar to those given by the phytosterols. This same substance has been isolated from the drug Euonymus atropurpureus.

The seeds contain a trace of the same alkaloid but no α-elaterin. No evidence could be obtained of the presence in colocynth of β-elaterin, which constitutes the physiologically active constituent of the fruit of Ecballium elaterium.

As a result of this investigation it would appear that the so-called " colocynthin " of previous investigators is a mixture of citrullol and the alkaloidal principle.

When manipulating colocynth extracts in solution according to the scheme of analysis for obtaining qualitative reactions, an extract will be obtained by shaking out the acid solution with ether, which will give a yellow-brown color with concentrated sulphuric acid, a dirty-red to cherry-red with Froehde's reagent, and a red, also pink to deep crimson with ammonium vanadate and the first color obtained in the last test will show blue in thin layers.

The basic or alkaloidal constituent of colocynth is of little value as an aid in detecting colocynth in mixtures on account of the small quantity occurring in the drug, and because its chemical properties are not well defined. If a sufficient quantity can be extracted and its purgative action tested on animals, a strong positive indication of the presence of colocynth would be established. But as colocynth is dispensed to such a large extent with Hyoscyamus, the mydriatic alkaloids will almost completely mask the colocynth bases.

The analyst will be obliged to depend upon the isolation of intensely bitter residues by an ether extraction of an acidulated aqueous extract of the alcohol soluble portion of the medicine under examination, and to diagnose the presence of colocynth by a careful observation of the color reactions performed on these residues. On rendering the acid solution alkaline the alkaloidal constituent is removed by agitation with chloroform.

The alcoholic soluble portion of the medicine, after washing with water to obtain the above-mentioned solution, will probably be a resinous mass which on careful treatment with absolute alcohol may leave a small portion of α-elaterin undissolved, and which on crystallization from absolute ether may be identified by its melting-point. This evidence is not necessarily conclusive of the presence of colocynth, because the absence of β-elaterin should be established, otherwise it may transpire that commercial elaterin, or Elaterium, is present in the mixture.

That portion of the resin soluble in absolute alcohol will be found to have a purgative action if submitted to a physiological test, but this evidence is of no value in establishing the presence of colocynth in mix-

tures, because the purgative principles of scammony and some of the other cathartic drugs which usually accompany colocynth reside in resins which will appear at this point and are soluble to a greater or lesser extent in alcohol.

Colocynth extracts are not precipitated by iron salts, neither do they give any color reactions with the same reagent because no tannins are present, and the drug is one of a very few that does not contain some tannin-reacting substance.

Quassia

The wood of Picræna excelsa (Simarubeæ) contains a bitter substance or group of substances to which the name quassia is given. The drug is a bitter tonic and is employed in cases of impaired digestion to tone up the stomach, and is usually combined with iron, Nux Vomica, magnesium sulphate, or gentian. The wood is sometimes turned into cups which can be filled with water and the liquid imbibed for its bitter and tonic action. Strips of porous paper saturated with quassia syrup are used for fly poisons.

The drug appears to have been obtained from two plants of the same genus, the original quassia coming from Quassia amara (Picræna amara), a small branching tree or shrub of Surinam, West Indies, northern South America, and some tropical parts of the Old World. The P. excelsa, which supplies the present commercial drug, is a large forest tree native of Jamaica and the Caribbean Islands.

Quassia occurs in cylindrical billets of various sizes and lengths, frequently accompanied with a light-colored sweetish, slightly adherent and bitter bark. Again it will be found in splinters or chips.

Quassin is apparently a composite substance, analogous in this respect to commercial elaterin. It crystallizes in oblique rhomboidal needles with a pearly luster. It is odorless, but has a bitter taste. Its melting-point is 210° C. and on cooling it forms an amorphous mass. It is soluble in about 400 parts of water at 15° C.; in 30 parts alcohol (85 per cent) and in 21 parts of cold chloroform. It is very soluble in boiling alcohol, in acetic acid, and very slightly soluble in ethyl and petroleum ethers. It is soluble in concentrated acids and alkalies, but not in alkaline carbonates. Continued action of alkalies forms resins. It is dextrorotatory in its chloroform solution; 4.22 gm. in 100 mils chloroform rotating the plane of polarized light to the right with a specific rotation of plus 38° 8′. Solutions of quassin are neutral.

It dissolves to a colorless solution in concentrated sulphuric acid, which becomes red on the addition of sugar.

It is precipitated by tannin from aqueous solution, but not by neutral or basic lead acetate, iodine, iron, or potassium mercuric iodide.

Quassin may be removed from an aqueous acid solution by chloroform and the residue left on evaporating the solvent subjected to the color test with sulphuric acid and sugar. Concentrated sulphuric acid alone produces no color.

Allen has suggested a reaction with bromin water, which is of value in identifying quassin and in detecting it in presence of other bitters. The residue is dissolved in chloroform and shaken with an excess of bromin water, the chloroform solution separated and shaken with ammonia. The color due to bromin will immediately disappear and if quassin be absent both the solvent and ammonia will be colorless, but in presence of quassin the chloroform will be colored bright yellow.

Quassin has been separated into two components, α- and β-picrasmin. The alcoholic extract is neutralized with magnesia, then acidified with tartaric acid, and the alcohol distilled off. The residue is shaken up with chloroform and the solution evaporated to syrupy consistency and dissolved in a mixture of equal parts of absolute alcohol and ether. This solution is evaporated and the residue dissolved in as little absolute alcohol as possible, the solution covered with a layer of ether and allowed to evaporate. The crystals which form are recrystallized from alcohol. The product thus prepared consists of two bitter principles, α-picrasmin ($C_{35}H_{48}O_{10}$), melting at 204° C., and β-picrasmin ($C_{36}H_{48}O_{10}$), melting at 209–212° C.

Simaruba Bark

The bark of the root of Simaruba officinalis was formerly recognized in the Pharmacopœia. The plant is a large tree closely allied to the quassia, and the drug contains a bitter principle which may be related to quassin. The bark contains a fixed oil, resinous material, a crystalline bitter substance, a crystalline non-bitter substance, gallic acid and a fluorescent principle. The tree grows well in Jamaica. S. amara is indigenous to Brazil and Guiana and S. glauca to the West Indies and Central America.

Simaruba has a limited use as a bitter tonic and in solution might readily be mistaken for quassia except that it contains gallic acid, which gives a precipitate with iron salts. However, this difference is of little importance analytically as the bark of quassia may be admixed with the wood of the official drug and it is not unlikely that gallic or tannic acid would be present in the bark.

Juglans. Butternut root-bark

The root-bark of Juglans cineraria (Juglandaceæ) has a mild cathartic and tonic action and is often present in mixtures intended to relieve constipation and biliousness. As a general thing it is mixed with Podo-

phyllum resin, colocynth, Hyoscyamus, Cascara sagrada, Nux Vomica, gentian, Apocynum, senna, and Rochelle salt in some combination or other, and certain special types of preparations contain the extract of butternut with manganese iodide, Sanguinaria, Hyoscyamus, and Veronica virginica; and with Podophyllum resin, Cimicifuga, Veronica virginica, and Capsicum.

A concentrated extract of the drug consisting chiefly of the resinous constituents is marketed as juglandin.

Coto

Coto and Para coto barks are closely allied drugs of uncertain botanical origin from Bolivia and Brazil.

Coto and its characteristic principle, cotoin, are used in diarrheic conditions, for cholera and rheumatism and as stomach tonics.

Cotoin, $C_6H_2(OH)_2(OCH_3)COC_6H_5$, crystallizes in pale yellow laminated crystals, but it is usually marketed as a crystalline powder. It has a pungent taste, melts 130–131°, is sparingly soluble in cold water, more readily in hot water, very soluble in alcohol, chloroform, benzol, ether, acetone, and carbon bisulphide, but insoluble in petroleum ether. It is removed from its acid solution by ether.

Cotoin crystals, when treated with concentrated sulphuric acid, turn orange, and the solution becomes bright yellow. Concentrated nitric acid produces an immediate blue color, soon changing to black and finally orange brown, with considerable chemical action. This is a very characteristic test. An aqueous solution of cotoin is colored violet brown by ferric chloride.

Para Coto

Para coto is used like coto as an appetizer and for diarrhea, dysentery, and similar disorders.

The chief constituent of Para coto is paracotoin, an indifferent crystalline, bitter principle, hydrocotoin, methyl hydrocotoin, protocotoin, methyl protocotoin (oxyleucotoin), phenyl coumarin, piperonylic acid, volatile oil, resin, and tannin.

Para coto is distinguished from coto by the action of nitric acid on the ether extractive matter. In the case of Para coto the result is the formation of a yellow color and in the case of coto a red color appears.

Paracotoin, $C_{12}H_8O_4$

Para coto is extracted with ether and the ether extract distilled. The residue is fractionated by repeated crystallizations from hot alcohol. The first body to separate out is paracotoin.

Paracotoin is a pale yellow, crystalline body, neutral in reaction, tasteless and odorless, melting at 149–152° C. It is difficultly soluble in water, but easily in ether, chloroform, and boiling alcohol. Concentrated sulphuric and nitric acids dissolve it, forming a yellowish-brown solution. On boiling with a solution of caustic alkalies, a colorless crystalline body, melting at 82–83° C. and having the odor of coumarin is formed; this body is acetopiperon (para-cumarhydrin), $C_9H_8O_3$ or $C_6H_3O_2CH_2 \cdot CO \cdot CH_3$, and paracotoic acid, $C_{12}H_{10}O_5$, a yellow amorphous mass melting at 108° C. Paracotoin fused with potassium hydroxide yields principally piperonylic acid, $C_8H_6O_4$.

One gram of paracotoin shaken up with 10 mils of fuming hydrobromic acid forms a semi-solid mass of yellow crystals, which on drying over potassium hydroxide lose hydrobromic acid. This residue decomposes with water and when recrystallized forms paracotoin, recognized by its crystalline form and melting-point.

By gradually adding about 1 gm. paracotoin to about 10 mils concentrated nitric acid, a red-brown solution will result, which, when heated for a short time on the water-bath and cooled, deposits a yellow crystalline mass. This product recrystallized from acetone and then from benzene or glacial acetic acid, forms golden-yellow crystals, melting at 195° C. This body is dinitro paracotoin, probably of the formula

$$C_{12}H_6(NO_2)_2O_4.$$

An excess of bromin added to a 10 per cent solution of paracotoin in choloroform cooled to 0° C. produces a deep yellow precipitate, which loses hydrobromic acid, and when recrystallized from alcohol forms the mono-bromide of paracotoin ($C_{12}H_7BrO_4$), melting at 200–201° C.

Fortoin is methylene dicotoin or cotoin formaldehyde.

CHAPTER XI

PURGATIVE DRUGS

THE ANTHRAQUINONE DRUGS

THERE are several well-known drugs which are conveniently considered together because they all contain derivatives of anthraquinone and because their physiological properties are more or less alike. They are aloes, senna, Cascara sagrada, buckthorn, rhubarb, and chrysarobin. Aloes also contains certain well-defined principles known as aloins. The individual drugs, their properties and components will be discussed separately and a general discourse on their recognition in mixtures will follow.

ALOES

Aloes is a resinous exudation from the wounds of different species of the genus Aloe (family Liliaceæ). Commercially there are two important varieties, the Barbadoes and Socatrine, with others of lesser moment. The former, also known as Curaçao aloes, is derived from A. chinensis and A. vera, and probably other species, and the latter, which is sometimes termed Zanzibar aloes, comes from A. Perryi. Natal aloes, from an unknown source, has almost disappeared from commerce. Cape and Uganda aloes from Cape Colony are derived from A. ferox. Hepatic aloes was the name originally applied to an East Indian aloes of a reddish-brown or liver color, but it is now used to designate certain sorts of dark opaque liver-colored Socatrine aloes.

In medicinal products both aloes and aloin are extensively employed, the mixtures containing them being chiefly purgatives, tonic laxatives, emmenagogues, restoratives, and laxative cold mixtures. They are usually dispensed in the form of pills and tablets. The standard liquid preparations, fluid aloes, contain licorice and sometimes myrrh; and the compound liquid aloes contains in addition to these, saffron, cardamom comp., and potassium carbonate. Aloes is also present in the liquid benzoin compounds with benzoin, storax, and tolu.

In pill and tablet mixtures aloes will be found combined with soap; soap and asafetida, sometimes with confection of rose leaves; ferrous sulphate or Blaud's mixture with or without Nux Vomica; rose leaves and

mastic; sometimes with rhubarb (dinner pills), aromatic powder, and myrrh; belladonna and Nux Vomica and ipecac; iron, arsenous acid, and strychnin; Hyoscyamus, colocynth, and tartar emetic; rhubarb, ipecac, and Nux Vomica; Podophyllum resin; Capsicum and Nux Vomica; mercury mass, rhubarb, and colocynth; gamboge, Podophyllum, Capsicum, and croton oil; colocynth, Podophyllum, soap, scammony resin, and cardamom (vegetable cathartic); colocynth, scammony resin, potassium sulphate, and clove oil; ergot extract, savin oil, black hellebore, and ferrous sulphate, sometimes with cotton-root bark, saffron, turpentine or pennyroyal oil in emmenagogue mixtures; cimicifuga racemosa, ferrous sulphate and cotton-root bark; gentian, rhubarb, and caraway; mercurous iodide, Podophyllum resin, Hyoscyamus and Nux Vomica; inspissated ox gall, stramonium, and berberin; ox gall, pepsin, ferrous sulphate, and Nux Vomica; sometimes with quinin; rhubarb, myrrh, and peppermint oil, sometimes with soap; quinin, calomel, Capsicum, aconite, ipecac, and opium; and others of similar composition. Aloin will be found in mixtures of the same general type. Some of the standard formulas are composed of aloin, strychnin, and belladonna, to which may be added Cascara sagrada, ipecac, Podophyllum resin, and ginger.

Aloes responds to several color reactions and the same reagent often reacts in a different way with the different varieties, thereby furnishing a means of characterizing them.

Borntrager's test consists in shaking with benzol an aqueous solution of the drug, or an aqueous solution of an evaporated alcoholic extract, and after separating the benzol solution, agitating with ammonia, when, on standing, a pink color, varying in intensity and shade, will develop. This reaction is also known as the emodin test and is obtainable with all drugs containing anthraquinone derivatives. The pink shade is usually the least intense with aloes and after a little experience, the rapidity with which the color appears and its shade and intensity will enable the analyst to distinguish an aloe reaction from that of other drugs.

Klunge's test consists in treating a very dilute aqueous solution of aloes with 1 drop of copper sulphate solution followed by sodium chloride and alcohol. The copper sulphate intensifies the yellow color and the salt and alcohol produce a red tint. Barbadoes and Curaçoa aloes give a deep red, Socatrine gives various shades of red and sometimes no color, Natal aloes, a faint red, and the hepatic varieties usually no color.

In Cripp's and Dymond's test a small quantity of the substance is triturated in a porcelain dish with 16 drops of concentrated sulphuric acid, 4 drops of strong nitric acid added and about 25 mils of water. A deep-orange to crimson color will result according to the kind of aloes present, and this color is intensified by adding ammonia. Barbadoes and Curaçoa varieties give crimson colors intensified to deep claret, Natal

deep crimson to intense brownish red; Socatrine and hepatic pale crimson or orange to claret.

Fluckiger's test, which is apparently characteristic of Natal aloes, is obtained by triturating with concentrated sulphuric acid and exposing to nitric acid vapor, when a deep-blue color will develop. Other varieties will sometimes give a faint blue or bluish-green color.

Stacy [1] reports that a cold aqueous extract of Barbadoes aloes gives a pink coloration with potassium ferrocyanide. The solutions must be so adjusted that neither is in excess. In most cases the color appears after five to fifteen minutes and more rapidly on boiling. In more concentrated solutions the color is deep crimson or blood red. The substance giving the reaction is only slightly soluble in petroleum ether, benzol, and chloroform, and insoluble in ether and ethyl acetate. Socatrine and Cape aloes and commercial aloin give a green color, while aqueous extract of Cascara sagrada and rhubarb do not give any reaction. The color yielded by Barbadoes aloes is destroyed by acids and excess of alkalies; small quantities of alkalies intensify the reaction, at the same time modifying it by the introduction of a brown tint.

An aqueous solution of borax produces a green fluorescence with aloes which is visible at considerable dilution. In the U. S. P. test 1 gram of the drug is intimately mixed with 10 mils of water. One mil of this solution and 100 mils of water are treated with a 20 per cent borax solution to obtain the reaction. Cascara gives a similar reaction, but only in a fairly concentrated solution.

If an aloes residue is acidified and extracted with ether, the ether separated and shaken with the borax reagent, the green fluorescence will develop in the aqueous layer. The appearance of the fluorescence is often retarded, sometimes an hour will elapse before it becomes apparent.

Aloes contain as their most characteristic constituents, aloe-emodin and aloin. The resinous material present yields cinnamic acid, aloe-emodin, and sugar upon acid hydrolysis, and *p*-cumaric and cinnamic acids on alkaline hydrolysis indicating that glucosides are present. Tschirch and Hoffbauer state that Curaçao aloes yields only cinnamic acid and Zanzibar aloes only *p*-cumaric acids, but Tutin and Naunton obtained both acids from the Curaçao variety. E. M. Bailey reports the presence of chrysophanic acid.

The aloin of Barbadoes aloes probably has the composition $C_{16}H_{18}O_7$ ($C_{21}H_{20}O_9$ or $C_{20}H_{18}O_9$, Seel and Kelber) $(\alpha)_D - 8.3°$ in 90 per cent alcohol, crystallizing in pale yellow prismatic needles, which are intensely bitter and after drying at 100° melt 145–150°, slightly soluble in cold water, but readily on boiling, slightly soluble in ether, chloroform, carbon bisulphide, benzole, and petroleum ether, and quite easily in alcohol, acetone,

[1] Analyst, 1916, 41, 75.

and acetic acid. It forms a tribrom-derivative melting 191–192°, which in turn yields a tetra-acetyl derivative melting 135°, from which it is assumed that barbaloin contains three hydroxyl groups. Its structural formula has not been determined with certainty. It dissolves in ammonia or alkalies to a deep orange-red solution with fluorescence. On adding ammonia and calcium chloride a precipitate is obtained.

Alcoholic solutions of aloin are neutral to litmus. Their aqueous solutions are colored green or greenish-black by ferric chloride and are gradually precipitated by basic lead acetate.

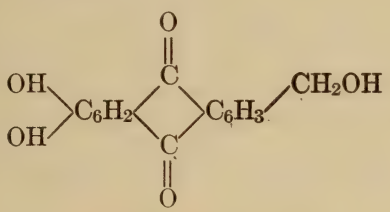
When boiled for twenty-four hours with an alcoholic solution of hydrogen chloride it yields a trihydroxymethylanthraquinone, isomeric with the emodin from rhubarb and senna.

Two isomeric barbaloins, the α and β, have been reported, the former being reddened in the cold by nitric acid, and the latter only on warming and in this particular resembling the nataloin of Natal aloes. Nataloin has thus far yielded no bromo-derivative. It contains a methyl group. It therefore differs from the barbaloins.

The commercial aloin is obtained chiefly from the Curaçoa and Barbadoes aloes.

ALOE-EMODIN

Aloe-emodin is an hydroxymethyldihydroxyanthraquinone, probably represented by the structural formula



It is closely related to chrysophanic acid which is a dihydroxymethylanthraquinone, and to emodin, which is a trihydroxymethylanthraquinone or hydroxychrysophanic acid.

Aloe-emodin crystallizes in orange-red needles melting 216–218° (224° Beal), sublimable, slightly soluble in water, from which it may be removed by immiscible solvents, and dissolving readily in alcohol, ether, benzol, alkalies, and glacial acetic acid. Its solution in alkalies is pink to deep crimson in color, depending on the quantity present. It is much more soluble in water when it is present with other constituents occurring in the drug, than in the separated and purified state. It gives a pink color with concentrated sulphuric acid and a pink to reddish-pink with Froehde's reagent.

Aloe-emodin dyes wool yellow from an acid bath, the color is stripped by ammonia and on acidulating the alkaline solution a second dyeing may be obtained. An alcoholic solution of emodin on evaporation with ferric chloride leaves a yellow residue; phenolphthalein under similar conditions leaves a pinkish residue with an odor of phenol, the color disappearing on cooling or in presence of moisture. Phenolphthalein imparts no color to wool.

The presence of aloes in a medicinal preparation is usually apparent by the characteristic odor. If the pill or tablet is extracted with alcohol and the solvent evaporated, the odor of aloes will often pervade the entire room, and the residue will appear as a deep red varnish. This residue can then be submitted to the tests described above.

Aloin alone is not detected as readily as the drug, but as the commercial substance often contains aloe-emodin, a weak Borntrager reaction may indicate the presence of aloin. As aloin is not removed to any extent from aqueous solution by immiscible solvents, and as it is not stable in the presence of alkalies it will often pass unnoticed. But if there is reason to suspect its presence a hot aqueous solution of the alcoholic extract should be filtered from any resinous matter, evaporated to dryness, extracted with absolute ether or chloroform to remove easily soluble acids, and then treated with hot alcohol and filtered from any undissolved sugar. On evaporation of the alcohol, the aloin will be left as a yellow residue and can be identified by its intense bitterness, reaction with nitric acid, and by the color reaction of its aqueous solution with ferric chloride, precipitation with bromine, slow precipitation with basic lead acetate after any tannins have been thrown out by neutral lead acetate, and precipitation of its ammoniacal solution by calcium chloride.

In performing the iron test, if a trace of the reagent is added at first, a reddish-violet color is obtained, and then on adding a larger quantity the greenish-black color appears. If the bromine water is added drop by drop at half-minute intervals a violet-red color appears at first, and this changes to yellow after an excess has been added with the appearance of a yellow precipitate.

Nataloin give a blue color with sulphuric acid and vapor of nitric acid.

Compounds or so-called derivatives of aloin are sometimes offered for sale with the claim that they possess certain novelties or advantages over the parent drug. The well-known carbonic ether derivative is one of them, and by boiling aloin with a persulphate a powder is obtained which is claimed to have purgative properties. Formaloin is a condensation product of formaldehyde and aloin.

RHUBARB

The well-known drug rhubarb is the rhizome of several species of Rheum (Polygonaceæ). The commercial varieties are known as Chinese, Canton, and Shensi, and are obtained from R. officinale, R. palmatum, R. palmatum tanguticum, and probably others. R. raponticum yields the English or Austrian variety known as rhapontic rhubarb.

Rhubarb is a popular remedy and will be found widely distributed in medicinal products. It has cathartic, tonic, and astringent properties, and is principally used in preparations designed to correct bowel and stomach troubles. In liquid form it is often combined with senna and licorice; with potassium carbonate or bicarbonate, cinnamon, Hydrastis, and oil of peppermint; the latter type often containing pancreatin or papain; aperient mixtures will contain magnesium acetate and rhubarb. Among the pill and tablet combinations may be mentioned those in which powdered rhubarb or its extract is associated with Cascara sagrada, Nux Vomica and aloin; ipecac, and aloes; Hyoscyamus, colocynth comp. and caraway; asafetida and iron; mercury mass, aloes, and colocynth comp.; calomel, Hyoscyamus, and colocynth comp.; alap, Jamaica ginger, colocynth comp., gamboge, and calomel; Podophyllum, Hyoscyamus, Capsicum, and aloes; calomel, oap, and aloes; mastic and aloes; Ignatia, Cinchona, and Capsicum; gentian, aloes, and caraway oil; mercury mass and sodium bicarbonate; myrrh, aloes, soap, and peppermint oil; strychnin, ipecac, and capsicum; opium, ipecac, and soap; ipecac, sodium bicarbonate, and peppermint oil, sometimes with Cascara; magnesia; opium, Capsicum, camphor, and peppermint oil in Sun cholera mixture. Warburg tincture is composed of rhubarb, angelica seed, Inula, saffron, fennel, gentian, zedoary root, cubeb, myrrh, white agaric, camphor, quinin sulphate, or cinchonin and cinchonidin and aloes.

The powdered drug has been found adulterated with turmeric and hematoxylin.

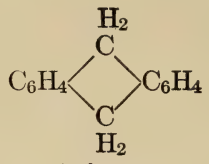
For the detection of rhapontic rhubarb, 10 grams of the powdered sample are boiled for half an hour with 50 mils of dilute alcohol, filtered, the filtrate evaporated to 10 mils, and after cooling shaken with 15 mils of ether. After standing for twenty-four hours the extract from official rhubarb will be clear, while that from the rhapontic variety will have deposited a crystalline sediment which appears under the microscope to consist of neddle-like prisms. The crystalline precipitate is filtered, washed with water, and dried and on treatment with concentrated sulphuric acid gives a purple-red color changing to orange.

In testing for turmeric 1 gram of the powder is mixed with 1 gram of boric acid, moistened with 10 mils of dilute sulphuric acid and spread out on a porcelain plate. On drying a purple-red color develops if turmeric is present, but pure rhubarb give only a brown or brownish-red shade.

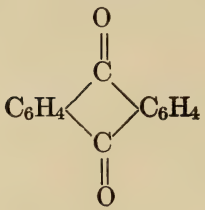
The chemistry of rhubarb has been the subject of extended research. Tutin and Clewer [1] separated a small quantity of an essential oil which gives the drug its characteristic odor, and in the aqueous extract cinnamic and gallic acids, rhein, emodin, aloe-emodin, emodin monomethyl ether, chrysophanic acid, and rheinolic acid, a crystalline mixture of glucosides of the above-mentioned anthraquinone derivatives, dextrose, levulose, tannin, and an amorphous non-glucosidic resin which represented the chief purgative constituent. The resin on hydrolysis gave all of the above derivatives, together with a new compound, a trihydroxydihydroanthracene, $C_{14}H_{12}O_3$, melting 256°. The portion of the alcoholic extract of the drug which was insoluble in water, when treated with various alkalies, yielded a further quantity of the anthraquinone derivatives, several fatty acids, a hydrocarbon melting 64°, a phytosterol (verosterol), glucosides similar to those above mentioned and amorphorous products.

The gallic acid present amounted to over 2 per cent, rhein 0.12 per cent, rheinolic acid 0.003 per cent, emodin 0.78 per cent, aloe-emodin 0.16 per cent, emodin mono-methyl ether 0.22 per cent, chrysophanic acid 0.49 per cent, glucosides 2 per cent, and non-glucosidic resin 10.4 per cent.

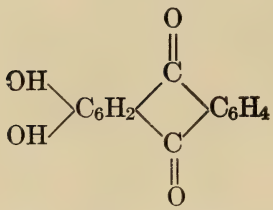
The relationship of the anthraquinone derivatives is apparent from the following structural formulas:



Anthracene

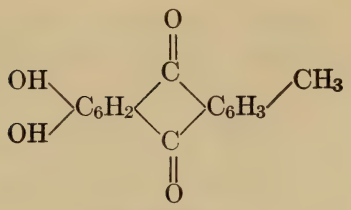


Anthraquinone

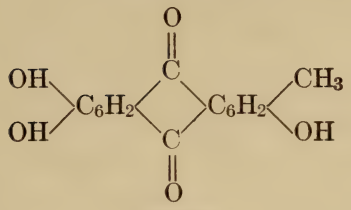


Alizarine (Dihydroxyanthraquinone)

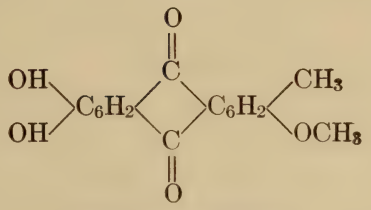
[1] Trans. Chem. Soc., 1911, 99, 946



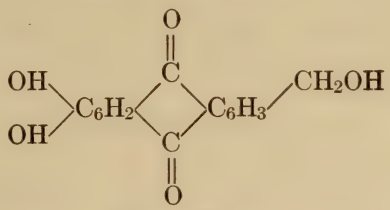
Chrysophanic Acid



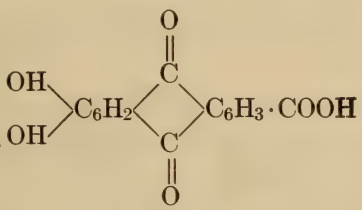
Emodin



Emodin Monomethylether



Aloe-emodin



Rhein

CHRYSOPHANIC ACID

This substance crystallizes from ethyl acetate in deep golden-colored spangles melting at 191° C. (198° Beal). In the purified state it is slightly soluble in water and alcohol, but dissolves readily in chloroform, benzol,

and ether. From an acidulated aqueous extract of a drug it may be completely removed by ether, and 5 per cent caustic alkalies extract it from its ethereal solution, giving rise to a beautiful purple-red liquid. Its diacetyl derivative melts 204°.

Commercially, chrysophanic acid is confused with rhein, both substances being considered identical. The same term is also applied to purified or oxidized chrysarobin from Goa powder, a substance deposited in the wood of Andira araroba. In this form it is used an as alterative and antiparasitic, and in ointment form is employed in psoriasis, herpes, and hemorrhoids.

If a solution of chrysophanic acid in alkali is heated with a little zinc dust, the red color changes to yellow, due to the formation of a reduction product. Reoxidation takes place readily by dilution with water and the addition of a drop or two of hydrogen peroxide. An alkaline solution of phenolphthalein is reduced by zinc and the color is not restored by peroxide.

EMODIN

Emodin crystallizes in deep orange needles melting 252°. Its triacetyl derivative melts 192° C. It is soluble in the organic solvents, and is removed from ether or chloroform by alkalies, forming pink solutions.

Emodin can be separated from chrysophanic acid by dissolving a mixture of the two substances in chloroform and shaking out with sodium carbonate, which will remove the emodin, leaving the chrysophanic acid to be extracted with potassium hydroxide.

EMODIN MONOMETHYL ETHER

This substance melts 195° and forms a diacetyl derivative melting 186°. It may be converted into emodin by heating to 160° with concentrated sulphuric acid.

Aloe-emodin has already been described under Aloes.

RHEIN

Rhein is a true acid, and is not readily soluble in the ordinary organic liquids, but dissolves in organic bases such as pyridin and anilin. It forms an orange-colored crystalline salt with pyridin which loses pyridin on heating to 130°. Rhein melts 318°. Its diacetyl derivative, which is produced on heating with a large excess of acetic anhydride in presence of a little camphorsulphonic acid or pyridin, melts 258°. Diacetylrhein may be removed from its solution in immiscible solvents with sodium carbonate on account of its containing a carboxyl group. When heated with xylene it first dissolves, then suddenly separates on boiling, and in

this form is practically insoluble except in alkalies. Rhein dissolves in concentrated sulphuric acid with a red color and is precipitated on dilution.

RHEINOLIC ACID

Tutin and Clewer [1] separated this acid from rhein by pouring a pyridin solution of the two substances into ether and filtering from the precipitated rhein compound. The ethereal solution yielded the rheinolic acid pyridin compound when shaken with ammonium carbonate. On drying to 130° pyridin was dissipated and the free acid melted 295–297°.

It is evidently an anthraquinone derivative. It dissolves in both alkalies and concentrated sulphuric acid with an intense red color, but differs from rhein by not being precipitated from the later solvent on adding water.

Its constitutional formula has not been determined.

The chief purgative principle of rhubarb is a non-glucosidic resin which Tutin and Clewer found present to the amount of about 10–11 per cent. Of the anthraquinone derivatives only aloe-emodin and chrysophanic acid have any physiological acitivity the mixture of the glucosides being quite inert.

Adulteration of rhubarb with turmeric and hematoxylin can be detected by preparing an alcoholic extract of the product, diluted with water, acidified, and shaken out with ether. On transferring the ether solution to strips of white paper and drying, hematoxylin is indicated if strong hydrochloric acid produces a pink color, and turmeric if boric acid and dilute hydrochloric acid yield the characteristic red tint which is changed to blue by ammonia.

Beal and Okey [2] subjected a dilute alcoholic extract of rhubarb to successive shake-outs with 4 parts of ether, benzol, and amyl alcohol. The benzol solution gives a violet-red precipitate with concentrated ammonia. The other anthraquinone drugs will give a red color in the aqueous layer, but rhubarb was the only one which they found yielded a precipitate.

If the benzol solution is shaken with solution of lead subacetate, a yellow or orange precipitate is obtained which turns red with alkali. The precipitates of the other drugs remain white.

When the amyl alcohol solution is shaken with lead subacetate a red color is obtained. In the case of the other anthraquinone drugs no change takes place.

[1] Proc. Chem. Soc., 1912, 28, 13; 1913, 29, 285.
[2] J. Amer. Chem. Soc., 1917, 716.

SENNA

The leaves of Cassia acutifolia and C. angustifolia (Leguminosæ) are recognized as the official drug known as senna. C. Marilandica, the American or wild senna, also furnishes an unofficial drug which has a limited use in medicine.

C. angustifolia furnishes the Indian or Tinnevelly senna, and the leaves of a variety of this species growing in Arabia are known as Mecca or Arabian senna. The Peruvian senna is also derived from the same species. The Alexandrian senna comes from C. acutifolia, though by some authorities it is regarded simply as a variety of angustifolia. C. holosericia of Abyssinia is known as Aden senna. The leaves of C. obvata are often mixed with those of the other official species.

The pods of the senna plants are commercially important, and are employed for the same purposes as the leaves.

Senna is used in cathartic mixtures. The powdered drug is one of the components of compound licorice powder where it is mixed with sugar, sulphur, fennel, and powdered licorice root. Compound extract of senna contains also jalap, and coriander, and other liquid mixtures contain, in addition to senna, Taraxacum; Grindelia and rhubarb; Podophyllum, leptandra, and jalap; Spigelia, savine, and manna; rhubarb; sarsaparilla, licorice, sassafras, anise, and methyl salicylate, and sometimes potassium iodide; caraway and coriander; Cascara sagrada, leptandra, juglans, and tartar emetic. Tablet and pill formulas are not numerous, but are of the same type as those containing the other anthraquinone drugs. Powdered senna, Cascara sagrada extract, Podophyllum, and magnesia are components of some of the popular laxative tablets and lozenges sold extensively to the laity. The well-known mixtures of the "Castoria" type contain senna, pumpkin seed, chenopodium, anise, rochelle salt, sodium bicarbonate, honey, and sugar, flavored with oil of peppermint and methyl salicylate; and other popular syrups consist of extract of figs and senna with the addition of one or more of the drugs mentioned in the above combinations.

Senna leaves are sometimes mixed with the pods. Senna siftings are imported in large quantities and formerly were always heavily adulterated with sand, some shipments containing from 25–40 per cent.

Tutin [1] has made an exhaustive study of senna leaves and reviewed the researches of previous authors. He found that the only anthraquinone derivatives present were rhein and aloe-emodin. In addition to these well-defined constituents senna contains salicylic acid, a volatile oil possessing a characteristic odor, kaempferol, $C_{15}H_6O_2(OH)_4$, a flavone derivative; kaempferin, a glucoside of kaempferol and glucose; a mixture of

[1] Trans. Chem. Soc., 1913, 103, 2006.

the glucosides of rhein and emodin, isorhamnetin melting 302° C., and glucosides of which this is a component; resinous matter from which myricil alcohol, palmitic and stearic acids, a phytosterol and phytosterolin were isolated; and amorphous substances.

Kaempferol (1–3–4 trihydroxyflavonol) is extracted from acid aqueous solutions by ether, and may be extracted from ether by dilute sodium carbonate. As obtained from an extract of the drug it is usually contaminated with aloe-emodin, from which it may be separated by redissolving in ether and shaking out with dilute sodium carbonate. By repeating this treatment the aloe-emodin finally will be left behind in the ether. Kaempferol can be crystallized by concentrating its solution in slightly diluted alcohol. It forms bright-yellow needles, melting 274°, colored yellow by alkalies and giving a strong blue fluorescent solution with concentrated sulphuric acid. It yields tetra-acetylkaempferol which when crystallized from ether, ethyl acetate, or alcohol forms colorless needles, melting 119–120°, and when resolidified melts at 183°. This is probably due to the presence of solvent of crystallization, because if the crystals are dried at 110° until no further loss in weight occurs they melt sharply at 183°.

E. M. Bailey [1] considers that chrysophanic acid is a constituent of senna.

When an extract of senna slightly acidified is shaken with ether, the ether solution will give the Bornträger reaction. If the ether solution is agitated with saturated solution of nickel acetate, the aqueous layer will develop a red color. On separating and adding potassium hydroxide solution a violet precipitate forms. Beal and Okey find that this reaction is characteristic of senna. Rhubarb and frangula require the addition of alkali to produce a color change. Cascara gives an orange yellow which becomes dark red after adding alkali. Aloes gives yellow-brown.

Henna leaves are obtained from Lawsonia inermis (Lythrariæ) and are used in jaundice and for cutaneous disorders, including leprosy. They contain tannins and a yellow substance having powerful dyeing properties.

The drug is sometimes confused with senna.

CASCARA SAGRADA

The bark and fruit of certain species of the Rhamnaceæ contain anthraquinone derivatives and Cascara sagrada or sacred bark from R. Purshiana has attained great renown as a laxative drug.

The tree yielding the Cascara bark is indigenous on the western coast of the United States and its habitat extends north into British America.

The fluid extracts, both plain and aromatized, are extensively used

[1] Jour. Ind. and Eng. Chem., 1914, 6, 320.

in medicine, and modified forms of the extract in which the bitter principles have been removed or emasculated by magnesia, are of common occurrence. Cascara cordials contain Berberis aquifolium, and some of the compound extracts contain senna and aloin. Many firms offer a special preparation of Cascara under a fancy or trade-marked name, in which they claim to have removed the bitter and griping principles of the drug and preserved all of its laxative features. Some of these preparations are highly fortified with other laxative drugs and croton oil.

Cascara is combined with malt extract, and with iron peptonate and manganese. It occurs in elixirs with senna, leptandra, butternut, and rochelle salt.

In the form of pills and tablets Cascara will be found combined with aloin, strychnin (or Nux Vomica), and belladonna; rhubarb, Nux Vomica, and aloin; Podophyllum, colocynth, Hyoscyamus, butternut, Nux Vomica, gentian and Apocynum; belladonna, Capsicum, Nux Vomica, Euonymus, and Xanthoxylum; Podophyllum, strychnin, aloin, belladonna and ginger; Nux Vomica, belladonna, Podophyllum, and ipecac; Blaud's mass and Nux Vomica; sometimes with arsenous acid; quinin, reduced iron, strychnin, and arsenous acid.

It has been commonly asserted and generally believed, that Cascara bark must be stored for at least a year or two before it can be used, the claim being that fresh bark contains an enzyme which causes intense griping and which is destroyed on long standing. Jowett isolated an hydrolytic enzyme from the bark but found that it had no griping acid.

When properly cured, the drug is just as available for producing medicines when it is a month old as when it has been stored for a year or two.

The bark of Rhamnus californica sometimes enters into competition with the official drug. The tree occurs abundantly in the southern part of California, while Cascara is found sparingly in that locality. There are recognizable differences in the characteristics of the leaves of the two species, but the appearance of the barks is practically identical. Microscopically one will find structural differences sufficiently distinct to aid in the recognition of the drug; and when macerated with dilute alcohol, the powder of R. Purshiana appears yellow, that of R. californica purplish; with potassium hydroxide the former gives an orange-yellow color, the latter a blood red.

The chemistry of the bark has been the subject of extended research, but much of the work is of little scientific importance. The bark contains resinous material, but this does not appear in large quantity in any of the extracts used in medicine because those extracts are obtained by water percolation. The only definite anthraquinone principle which

Jowett isolated from the bark was emodin. He found no chrysophanic acid nor glucosides yielding emodin on hydrolysis. Iso-emodin has been reported. Syringic acid and rhamnol have been reported.

An aqueous extract of the bark, after precipitation with lead acetate, contains substances which are thrown out by basic lead acetate and which subsequently, after removing the lead, yield emodin on hydrolysis. Dohme and Englehardt consider that basic lead acetate precipitates a glucoside, to which they give the name purshianin, but Jowett claims that he was unable to detect any glucosidic character in this body. In the course of his experiments with the extract the writer has isolated substances of a glucosidic nature, and while their chemical purity has not been established it appears probable that the bark contains anthraquinone derivatives of a more complex nature than emodin.

THE BUCKTHORNS

The bark of the stems and branches of the Alder buckthorn, R. frangula furnishes the official drug. The barks of R. cathartica, the common buckthorn, and of R. carniolica are probably sold for the official drug, as all of these shrubs grow in the same localities.

The berries of R. frangula yield a juice formerly sold as Rhamni Succus. This juice, and that of the berries of R. cathartica, is still used as an hydragogue cathartic in the form of a syrup in combination with ginger and pimento. The combination appears to be useful in dropsy, rheumatism, and gout.

The berries of these plants as well as those of R. infectoria and R. santiles are used for making yellow dyes.

The frangula barks contain anthraquinone derivatives. Both of the common buckthorns contain a glucoside to which the name frangulin has been given, and which on hydrolysis yields rhamnose and emodin. The emodin of the buckthorn and Cascara sagrada are identical. Frangulin resembles the glucosidic substances of Cascara. It is precipitated by basic lead acetate, copper acetate, barium hydroxide, and ferric chloride and gives a red solution with concentrated sulphuric acid. On hydrolysis it yields emodin and rhamnose. These drugs also contain flavanol derivatives soluble in concentrated sulphuric acid with a greenish-blue fluoresence. Rhein and chrysophanic acid have also been reported.

The anthraquinone derivatives exist in greater quantity in R. frangula than in R. Purshiana, but their general character appears to be the same. It is probable that there is but little difference in the chemical constituents of these drugs, though considerable research is still needed to clear up the disputed points concerning their chemistry.

Frangula bark gives a much stronger Bornträger reaction than Cascara

sagrada, in fact the shade is as deep a crimson as that given by senna or rhubarb.

When a dilute alcoholic extract of frangula is shaken with 4 parts of ether, and the latter agitated with saturated solution of nickel acetate no red color appears until potassium hydroxide is added to the aqueous layer when a deep red-violet precipitate is obtained, and the ether layer becomes colorless almost immediately. Cascara gives an orange-yellow before adding alkali; the latter then causes a dark red color. With rhubarb the ether layer remains colored for a much longer period.

GOA POWDER AND CHRYSAROBIN

Goa powder is an irritant material deposited in cavities in the trunk of the Vouacapoua Araroba (Leguminosæ), a tree growing in Brazil and probably other South American countries. The powder is also known as Brazil powder, ringworm powder, crude chrysarobin, and Pão de Bahia. When fresh it is light yellow and bitter, becoming darker on exposure to the atmosphere. It consists of chrysarobin, gum, resinous matter, and woody fiber, and is often adulterated with powdered Andira wood.

Goa powder is used as a remedy for skin diseases and for preparing chrysophanic acid.

It is called "Arariba" powder, but this name should be used only to distinguish the barks of Sickingia viridiflora and S. rubra, which are of a different family.

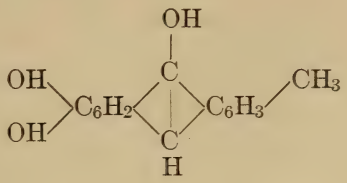
Chrysarobin is the name given to purified Goa powder obtained by extraction with chloroform. It is also called medicinal chrysophanic acid and is usually described as the neutral principle of the powder. This description is confusing as it is a mixture of several different substances, some well-defined and others not yet determined, and they are by no means all of neutral character.

Chrysarobin is an orange-yellow microcrystalline powder darkening on exposure, soluble in chloroform and benzol with ease, less readily in ether and alcohol and partly and with some difficulty in water. It is soluble in potassium hydroxide to a deep brownish-red solution inclining to purple. It dissolves in concentrated sulphuric acid to a deep red solution.

Tutin and Clewer[1] find that chrysarobin contains on the average about 5 per cent of chrysophanic acid, 2 per cent of emodin monomethyl ether, 46 per cent of the anthranol of chrysophanic acid, a small amount of the anthranol of emodin monomethyl ether, 18 per cent of dehydro-emodinanthranol-monomethyl ether, 4 per cent of ararobinol, $C_{23}H_{16}O_5$, and 25 per cent of an inseparable mixture and amorphous material.

[1] Proc. Chem. Soc., 1912, 28, 13, and 1913, 29, 285.

The anthranol of chrysophanic acid (chrysophanol), $C_{15}H_{12}O_3$, may be represented by the structural formula



It forms pale yellow leaves from chloroform, melting 204°. It is insoluble in aqueous alkalies. Its alcoholic solution gives a dark red-brown color with ferric chloride. When treated with chromic acid it is converted into chrysophanic acid. It gives an orange-red color with concentrated sulphuric acid.

Chrysarobin is chiefly employed as an external remedy in psoriasis, herpes tonsurans, and hemorrhoids. It is administered in the form of ointments, cerates, and collodion mixtures. For hemorrhoids it may be combined with iodoform and belladonna, and dispensed in vaseline ointments, or in glycerin or cocoa butter suppositories.

Acetates of chrysarobin are sold under the names of Lenirobin and Eurobin. The former is described by its makers as a tetracetate, and is soluble in chloroform, acetone, and benzol, but insoluble in water. The latter, a triacetate, dissolves in the same solvents, and is dispensed in acetone. It may be found combined with saligallol (pyrogallol disalicylate). They are used as substitutes for chrysarobin in skin diseases.

DRUGS OF THE RUMEX GENUS

The roots of Rumex crispus (Polygonaceæ), yellow or curled dock, and R. obtusifolius, bitter dock, are used medicinally. The former was official in the U. S. P. 1890. The roots of other species are probably sold indiscriminately with those of the two mentioned.

Yellow dock is an alterative, tonic, and mild laxative. It is administered in the form of a syrup combined with potassium iodide, magnesium sulphate, the bark of Celastrus scandens (False bittersweet), the bark and twigs of Parthenocissus quinquefolia (American ivy or Virginia creeper), and the root and plant of Scrophularia marilandica (Maryland figwort or carpenter's square). The solid extract is employed locally in skin diseases and the powdered root as a remedy for spongy gums.

The chemistry of the dock roots has never been thoroughly investigated, but anthraquinone derivatives are present, and it is claimed that emodin and chrysophanic acid have been identified.

The leaves of R. acetosella, the common sorrel or sour grass, are employed in febrile, inflammatory, and scorbutic affections as a refrigerant

and diuretic drug. They contain acid potassium oxalate and a little tartaric acid.

The root of Polygonum cuspidatum syn., Pleuropterus zuccarinii (Polygnaceæ) the Japanese knotweed, is reported as containing free emodin and anthraquinone glucosides. This root has been confused with that of P. bistorta, which is apparently the true bistort and which contains much tannin. Bistort is used in acute and chronic intestinal catarrh, dysentery, amenorrhea, and in hair preparations designed to promote the growth of the hair.

Methods for Identifying the Anthraquinone Drugs in Medicines.— It is obvious that there are several important drugs whose most prominent ingredients are anthraquinone derivatives and that in mixtures where they functionate as extracts, the absolute identification of one particular drug to the exclusion of all the others is not an easy matter. Furthermore it has been demonstrated that there are several other drugs which contain those or similar derivatives, but whose general chemistry is not known, and which might easily be mistaken for the more common varieties when dispensed in the extract form. The separation and identification of the anthraquinone derivatives is possible only when one has a considerable quantity of material, much more than is usually offered as a sample for the analysis of a medicine. In mixtures of powdered drugs the microscopic character of the fibers and cellular structure will aid the analyst in arriving at absolute results, but in liquid or solid extracts where the structural characteristics are lost, he must depend upon the odor, color reactions, and presence of other principles normally occurring in the plant in order to determine the identity of the drug in hand. Often he can go safely only so far in his conclusions as to assert that anthraquinone derivatives are present.

Preparations containing rhubarb will give a magenta coloration when subjected to the Bornträger reaction. Senna and frangula extracts also give intense crimson or magenta shades, while Cascara usually gives a lighter color more on the pink, and with aloes the color develops gradually.

The essential oil of rhubarb has an unmistakable and characteristic odor and will furnish valuable evidence in establishing the identity of the drug. If an alcoholic extract is mixed with water and distilled with steam, the oil passes into the distillate and is readily recognized. This same odor is always apparent when running an alcohol determination on liquid preparations containing rhubarb.

Gallic acid furnishes further evidence of the presence of rhubarb.

The fractionation and identification of each and every anthraquinone derivative is impracticable, when working with medicines and about all that one can accomplish is to obtain conclusive tests for their identity.

If aloes or aloin are simultaneously present with rhubarb, the odor,

presence of gallic acid and strong Bornträger reaction will distinguish the latter, while the odor of the aloes and identification of aloin as described under Aloes will distinguish the former.

Reliable tests for senna and the Rhamnus drugs in presence of rhubarb have been worked out by Beal and Okey. Senna contains salicylic acid, which is of course easily separated by petroleum ether from an acid aqueous solution of the alcoholic extract of the mixture, but while this is indicative of the presence of senna it is by no means conclusive. Its absence, however, indicates that there is no senna extract in the preparation, and is a point for the analyst to remember in case he is testifying and the cross-examiner seeks to confuse him regarding the identity of the components of the mixture in hand. Senna also contains kaempferol, which can be separated from the aloe-emodin of the drug as described and then subjected to proper tests for its identity. In ordinary cases under drug control laws it is a small matter analytically whether the drug present is absolutely identified or not. It is sufficient to assert that there was found a drug or drugs containing anthraquinone derivatives, and as these are of limited number and of similar physiological action it matters little analytically whether the formula is composed of one or all of them.

The quantitative estimation of the anthraquinone derivatives in these drugs or in mixed medicinal preparations containing no phenolphthalein may be accomplished according to the second method of assay given under Rhubarb, on page 62.

Bailey[1] differentiates between the anthraquinone derivatives by preparing an alcoholic extract of the sample under examination, evaporating the solvent, diluting with 25 mils of water, precipitating with lead acetate and filtering. The lead precipitate is transferred to a beaker and digested for one hour on a water-bath with 10 per cent sulphuric acid. The solution is filtered and while still hot, is extracted with benzol.

The benzol solution is washed first with 25-mil portions of 5 per cent ammonium carbonate until the washings are colorless or but faintly colored, then with similar portions of 5 per cent sodium carbonate until the washings become pink, and finally with 5 per cent sodium hydroxide. He found that ammonium carbonate removed anthraquinone derivatives which he did not identify, sodium carbonate removed emodin and sodium hydroxide removed chrysophanic acid. The three aqueous solutions are then separately acidified, shaken out with ether, and the ether residues examined directly or after recrystallization from alcohol.

A few drops of the ether residue is treated with 4 to 5 drops of concentrated sulphuric acid, then 1 to 2 drops of concentrated nitric acid, and, finally about 1 mil of water.

In the case of chyrsarobin a little color is removed by the first two

[1] Amer, Jour. Pharm., 1915, 87, 145.

reagents, but the bulk of the color goes into sodium hydroxide with one washing. The ether residue gives orange red with sulphuric acid, becoming yellow with nitric acid and giving a yellow solution and a flocculent precipitate with water.

With Rhamnus frangula most of the color is removed by the sodium carbonate and the ether residue gives an intense pink with sulphuric acid, becoming yellow with nitric acid and pink with water.

With rhubarb, both the sodium carbonate and hydroxide fractions are colored, the ether residue of the former reacted similarly to the emodin body derived from R. frangula, and the color test with the ether residue from the latter were the same as for chrysophanic acid from chrysarobin.

With senna, a considerable quantity of color goes into the ammonium carbonate fraction to an orange-colored solution, and on separation the residue obtained is not homogeneous, being partly insoluble in ether. The ether-soluble portion gives a purple or violet color with sulphuric acid, becoming yellow with nitric acid and remaining yellow on adding water. The ether-insoluble portion gives a purple-red solution with sodium hydroxide which is not discharged by zinc dust, and on dilution with hydrogen peroxide the color fades and a light-colored precipitate settles. Sodium carbonate and hydroxide remove coloring matter from the benzol and the residues finally obtained react for emodin and chrysophanic acid respectively.

With aloes, ammonium carbonate removes considerable color, the washings being orange colored. The ether residue gives a purple color with sulphuric acid, turning yellow with nitric acid and unchanged with water, corresponding to the substance obtained from senna. Sodium carbonate removes but a small quantity of material, and an ether residue gives a red to brownish with sulphuric acid, turning yellow with nitric acid and unchanged by water. The greater part of the color is removed by sodium hydroxide and the ether residue reacts similarly to the chrysophanic acid obtained from the other sources.

Phenolphthalein interferes with the Bornträger reaction and may be removed as the iodin compound by a method evolved by Warren.[1]

The preparation in the form of a thick syrup is diluted with water, faintly acidified, and filtered. The filtrate is evaporated to a thick syrup and, while still warm, is extracted with acetone slightly acidified with hydrochloric acid. The acetone extract is evaporated to dryness on a water-bath, the residue twice moistened with alcohol, and the alcohol evaporated in order to remove the last traces of acetone.

The residue is dissolved in dilute sodium hydroxide, iodin added, followed by hydrochloride acid, which precipitates tetraiodophenolphthalein. After cooling for an hour below 15° C., the iodin compound is

[1] Amer. Jour. Pharm., 1914, 86, 444.

filtered off, the excess of iodin removed by sodium sulphite, and the solution extracted with benzol to remove the anthraquinone derivatives.

One of the most important contributions to the chemistry of these drugs from an analytical standpoint was made by Beal and Okey and to which reference has been made several times in this chapter.

A small amount of a dilute alcoholic solution of the drug preparation is shaken with 4 volumes of benzol, separated and the benzol solution shaken with 30 per cent sodium hydroxide. A light red to deep violet color indicates anthraquinone drugs. If the color is due to phenolphthalein it will disappear quickly, that due to the other drugs will remain unchanged.

If the above test is positive, a portion of the benzol is evaporated, moistened with nitric acid and again evaporated. The residue will be red or orange-red, and when treated with potassium cyanide or 30 per cent alkali will take a red or purplish-red with anthraquinone drugs. Phenolphthalein gives a brownish color. If the latter is present it should be removed by the method of Warren.

The dilute alcoholic solution is then divided into three portions, A, B, C.

Portion A is shaken with 4 parts of benzol and subsequently with amyl alcohol. A portion of the benzol solution is shaken with concentrated ammonia, a deep red-violet color with a precipitate of the same color settling between the liquids indicates rhubarb. This is confirmed by the lead subacetate test, yellow-orange precipitate, turning red with alkalies. (If a concentrated alcoholic solution of the drug is precipitated with water, the resinous matter filtered off, washed, dried, and treated in a porcelain dish with alcohol, sodium peroxide, and water, a red color appears in the alcohol, turning orange-red on the addition of water. The other drugs impart no color to the alcohol, but yield various shades of orange with water.)

The amyl alcohol shake-out is divided to 4 portions. One portion is shaken with strong ammonia, and the development of a deep-red color and a dark green fluorescence indicates aloes and fresh Cascara. If positive, another portion is shaken with a saturated solution of mercurous nitrate containing a slight excess of nitric acid; in the presence of aloes a deep-red color develops in the aqueous layer, reaching its height in six to eight minutes, fading to reddish-brown. If a small quantity is present the color is pink. Another portion is evaporated, taken up with dilute alcohol and treated with copper sulphate and hydrogen peroxide and boiled, a red color will appear in presence of aloes. Another portion should be evaporated and tested with borax solution to obtain the characteristic green fluorescent solution. If Cascara is indicated, a portion is evaporated, the film moistened with nitric acid, evaporated to dryness, treated with stannous chlo-

ride containing a little free hydrochloric acid, decanted, washed with jet of water, and treated with alcohol; deep-red color indicates cascara; aloes gives yellow brown.

Portion B above is then shaken with 4 parts of ether and divided into several fractions. One portion is shaken with saturated solution of nickel acetate, and if the aqueous layer is red, senna is indicated. If the solution remains green and subsequently gives a green precipitate with potassium hydroxide, but preliminary tests have shown a permanent color with alkali, rumex is indicated. (The authors apparently used Rumex ecklonianus in these researches.) The reagent and the ether must be kept mixed when the alkali is added. When shaken with alkali, a violet precipitate will appear if senna is present; a red-violet precipitate with rhubarb or frangula; and a dark orange-red color with Cascara. Rhubarb and frangula give orange solutions before adding alkali. The ether layer after adding alkali, will become colorless almost immediately, except in presence of rhubarb, when it persists.

If conclusive evidence is not obtained, a portion of the ether solution is evaporated, nitrated, and treated with stannous chloride as above described. Senna gives a green residue; aloes brown; Cascara red; Rumex, rhubarb, and frangula violet-red; phenolphthalein lemon-yellow. The excess of stannous chloride should be removed with water, the residue treated with U. S. P. solution chlorinated soda, and if a red color appears senna is present.

PODOPHYLLUM AND PODOPHYLLOTOXIN

The well-known mandrake or May apple, Podophyllum peltaltum (Berberidaceæ), is a common plant of the rich woodlands east of the Mississippi. It grows in dense patches and is one of the most conspicuous plants in the early spring throughout its range.

The rhizome contains an irritant resin, sometimes called podophyllin, which is extensively used in remedies for liver and bowel complaints.

Podophyllum resin is one of the constituents of a great many formulas containing cathartic drugs, and will be found in various combinations with aloin, strychnin, or Nux Vomica, belladonna or Hyoscyamus, Capsicum, ipecac, Colocynth, jalap, scammony, gamboge, Cascara sagrada, juglans, gentian, leptandra, oil of peppermint, mercury mass, croton oil, soap, Veratrum, and Apocynum. It enters into the compound cathartic pills of the U. S. P. with colocynth comp., Hyoscyamus, jalap, leptandra, and oil of peppermint; it is combined with santonin, with calomel and sodium bicarbonate; with Hydrastis canadensis; with Euonymus; with Cimicifuga; with quinin or cinchonidin, arsenous acid, Gelsemium, pepper, and ferrous sulphate; and often it is dispensed by itself.

It is combined with castor oil in elastic capsules. Fluid extract mandrake compound contains extract of Podophyllum, senna, leptandra, and jalap; and it is present in fluid extract dandelion compound with Taraxacum and Conium.

One of its purified active principles, podophyllotoxin, is used quite extensively as a remedial agent.

The valuable constituent of the rootstock is a resin amounting to 3.5-5 per cent, containing podophyllotoxin and picropodophyllin, an isomeric substance. The former is slightly soluble in water, the latter insoluble in water. The resin is intensely irritant to the mucous membrane and, unless carefully handled, produces conjunctivitis.

The rhizome of P. emodi, a plant growing on the lower slopes of the Himalayas, is larger and yields 11-12 per cent resin, but is only half as rich in podophyllotoxin.

The chief constituent of the resin is podophyllotoxin, a neutral substance possessing the formula

$$C_{20}H_{15}O_6(OCH_3)_3+2H_2O, \text{ or } C_{15}H_{14}O_6+2H_2O,$$

crystallizing in prisms, melting 94° C. (117° reported), strongly lævorotatory. When heated with alkalies it is converted by hydration into the salt of an unstable gelatinous acid, podophyllic acid, $C_{15}H_{16}O_7$. This acid loses water and furnishes the crystalline picropodophyllin isomeric with podophyllotoxin, melting 227° and optically inactive. It passes again into podophyllic acid when warmed with aqueous alkalies. Podophyllotoxin and picropodophyllin furnish identical decomposition products; when oxidized with nitric acid, oxalic acid is the principal product; when fused with alkalies, orcinol and acetic acid are produced. Both substances contain three methyl groups and no hydroxyl.

The yellow coloring matter of the drug is identical with quercetin, the yellow coloring matter of quercitron bark. An amorphous resin called podophylloresin is present in the drug.

Podophyllotoxin is prepared commercially by digesting the resin with chloroform, filtering, concentrating to a thick syrup, and treating with alcohol-free ether as long as a precipitate is obtained. The clear liquid is then decanted and concentrated and the syrupy residue poured into petroleum ether, when the commercial podophyllotoxin is precipitated.

An extract of mandrake when subject to Bornträger's test gives a bright-yellow color with ammonia before boiling with acid and an amber color afterwards. This coloration is probably produced by the yellow coloring matter naturally present in the drug.

Determination of Resin in the Drug or Extract.—W. M. Jenkins[1] has based a method on the ready solubility of the resin in a mixture of

[1] J. Ind. and Eng. Chem., 6, 1914, 671.

alcohol-chloroform 1–2. Five mils of the fluid extract are shaken with 5 mils of alcohol, 10 mils of chloroform, and 10 mils of acidulated water (0.6 per cent hydrochloric acid). The lower layer is drawn off and the aqueous solution extracted twice with 15-mil portions of the alcohol-chloroform mixture. The united extracts are washed with 10 mils of acidulated water, and the aqueous layer again shaken twice with 15 mils of the solvent mixture. The combined extracts are evaporated and the residue at 100° C. weighed.

The drug is first extracted with alcohol by hot maceration and 10 mils of the extract, equivalent to 2 grams of the drug, are treated as described above except that the addition of 5 mils alcohol is omitted.

The determination of the podophyllotoxin is often important, but at present the methods in use leave much to be desired. There are two types of procedure, that of the Dutch Pharmacopœia and the lime method. The former gives about one and one-half times as much podophyllotoxin and is based on the difference in solubility in petroleum ether, after a chloroformic extraction, of the resin and the neutral crystalline principle.

The lime method really amounts to a conversion of the podophyllotoxin to the isomeric picropodophyllin and weighing it as such. The procedure recommended by Gordin and Merrell [1] is as follows:

Five grams of the resin and 10 grams of freshly prepared calcium hydroxide are placed in a strong, well-corked bottle of about 200 mils capacity and the whole weighed. The bottle is then uncorked, heated for a few minutes on the water-bath at 60–65°, 15 mils of alcohol added, the whole well shaken and the closed bottle kept on the water-bath for eight hours, shaking the first few minutes to prevent the formation of a hard lump and then every fifteen minutes. The bottle is then cooled, about 7 mils of chloroform added, then enough of a mixture of 2 parts alcohol–1 chloroform (by vol.) to make the whole liquid weigh 130 grams. After shaking for a few minutes the bottle is allowed to stand for twenty-four to forty-eight hours, 65 grams of the clear liquid drawn off into a tared dish, the solvent distilled off and the residue weighed.

JALAP AND SCAMMONY

Several species of plants belonging to the Convolvulaceæ contain purgative resins, which have an extensive medicinal use. The two most important are Exogonium purga (Ipomœa purga), which furnishes the dried tuberous root known as jalap, and Convolvulus scammonia, which furnishes the gum resin known as scammony. In addition, Ipomœa purpurea contains resinous constituents which are apparently similar, and is sometimes substituted for jalap resin, and the root of I. orizabensis

[1] Proc. Amer. Pharm. Ass., 1902; J. Soc. Chem. Ind., 1902, 1362.

(Mexican Scammony) has partially displaced true Scammony. Power and Rogerson[1] have reported an investigation of the tuberous root of I. horsfalliæ, but the resin therefrom was in small quantity and apparently devoid of physiological properties.

JALAP

The only constituent of the tuber possessing interest to the drug chemist is the resin. This is obtained by an alcoholic extraction of the ground drug, the residue left on evaporation the solvent being washed and dried. About 10 per cent of this resin is soluble in ether, and about 25 per cent is subsequently dissolved in chloroform. The U. S. P. standard of not over 30 per cent chloroform-soluble matter in resin of jalap is indefinite, as variable amounts are removable from the resin according to the method employed. When the resin is stirred with the solvent in the cold, it is not completely extracted after nineteen or twenty additions of chloroform, and the large number of fractions required renders the procedure impracticable. The quantity dissolved in the cold by this method is much less than that taken up by hot chloroform when the sample is subjected to a Soxhlet or Knorr extraction. In fact some samples of jalap resin yield over 90 per cent to the solvent, when subjected to the Soxhlet method.

The adulterants of jalap resin include colophony, guaiac, myrrh, Tolu balsam, and the resin from aloes, jalap stalks, and Fungus Laricis (Dieterich).

Jalap resin is used in several well-known cathartic mixtures dispensed in the pill or tablet form. In the liquid form, extract of jalap is combined with the extracts of Podophyllum, senna, leptandra in fluid extract mandrake compound; and with senna and coriander in fluid extract senna compound. The types of pill mixtures contain in addition to jalap resin, colocynth comp., colocynth, aloes, cardamom, scammony, soap, Podophyllum, Capsicum, and Hyoscyamus; leptandra, aloin, Podophyllum, gamboge, Capsicum, Hyoscyamus, and peppermint oil; similar formulas with Nux Vomica or gentian or calomel, or rhubarb; liver pills with aloes, gamboge, leptandra, Capsicum, Veratrum viride, croton oil, calomel, or Podophyllum; aloes, mercury mass, and tartar emetic; and the U. S. P. vegetable cathartic consisting of colocynth comp., Hyoscyamus, jalap, leptandra, Podophyllum, and peppermint oil.

The chief portion of jalap resin is insoluble in ether and is commonly designated as " convolvulin," and the ether soluble portion as " jalapin," though originally the latter term was applied to the chief portion of the resin, which was insoluble in ether. These terms have little significance

[1] Am. J. Pharm., 1910, 82, 355.

at the present time, however, as Power and Rogerson have published the results of a carefully conducted research, the essentials of which may be summarized as follows:

The total crude resin, when purified by means of animal charcoal, had a specific optical rotation of −37.0°. On extracting the crude resin successively with (I) light petroleum (b.p. 40–60°), (II) ether, (III) chloroform, (IV) ethyl acetate, and (V) alcohol, a number of products were obtained, the examination of which has shown the resin to be of much more complex composition than has previously been assumed.

I. **Petroleum Extract of the Resin.**—This represented 1.9 per cent of the total resin. It contained palmitic and stearic acids in a free state, and, after hydrolysis, yielded formic, butyric, and higher volatile acids, palmitic acid, and a mixture of unsaturated acids, which appeared to consist chiefly of linolic acid. From the unsaponifiable portion of the extract there were obtained a phytosterol, $C_{27}H_{46}O$ (m.p. 134–135°, $(\alpha)_D$ −32.4°), cetyl alcohol, $C_{16}H_{34}O$, and a small amount of a substance melting at 56–57°, which agrees in composition with the formula $C_{18}H_{36}O$. This substance, which appears to be a new compound, yields color reactions similar to those of the phytosterols.

II. **Ether Extract of the Resin.**—This represented 9.7 per cent of the total resin. From it there was isolated a small amount of a new, dihydric alcohol, which possesses the formula $C_{21}H_{32}O_2(OH)_2$, and is designated ipurganol. Ipurganol crystallizes in colorless needles, melting at 222–225°, and has, in pyridin solution $(\alpha)_D$ −44.9°. It yields color reactions similar to those given by the phytosterols. Diacetylipurganol, $C_{21}H_{32}O_4(CH_3 \cdot CO)_2$, forms colorless leaflets, melting at 166–167°, and has, in pyridine solution, $(\alpha)_D$ −36.0°. The ether extract, after treatment with alkalies and dilute sulphuric acid, yielded, furthermore, a little phytosterol and acetyl alcohol, small amounts of volatile acids, and a quantity of amorphous products.

III. **Chloroform Extract of the Resin.**—This represented 24.1 per cent of the total resin. From it there was isolated a very small amount of β-methylæsculetin, $C_9H_5(CH_3)O_4$. After treatment with alkalis and dilute sulphuric acid this extract yielded, furthermore, formic, butyric, and *d*-methylethylacetic acids, together with convolvulinolic acid, $C_{15}H_{30}O_3$, and apparently a higher homologue of the latter. Glucose was also produced by this treatment, thus indicating that a portion of the extract was of a glucosidic nature.

IV. **Ethyl Acetate Extract of the Resin.**—This represented 22 per cent of the total resin. On treatment with dilute alcoholic sulphuric acid, it yielded formic, butyric, and *d*-methylethylacetic acids, together with convolvulinolic acid, and apparently a higher homologue of the latter, having the composition $C_{17}H_{34}O_3$. It also yielded, besides indefinite

amorphous products, a considerable quantity of a sugar, which was evidence that at least a portion of the extract was of a glucosidic nature.

V. **Alcoholic Extract of the Resin.**—This represented 38.8 per cent of the total resin. After treatment with animal charcoal it was obtained in the form of a nearly white powder, which melted at 150–160°, and had $(\alpha)_D - 37.1°$. When fused with potassium hydroxide it yielded formic, acetic, butyric, valeric, and higher volatile acids, together with azelaic and sebacic acids. When subjected to alkaline hydrolysis with baryta it yielded, besides small amounts of formic and butyric acids, *d*-methylethylacetic acid, $C_5H_{10}O_2$ (b.p. 174–176°; $(\alpha)_D + 17.55°$), together with a quantity of an amorphous product, readily soluble in water, which may be designated as the hydrolyzed resin. This has now been shown to be of very complex composition, for by successive extraction with (*a*) ether, (*b*) chloroform, (*c*) ethyl acetate, and (*d*) alcohol it is capable of being resolved into a number of products.

(*a*) *Ether Extract of the Hydrolyzed Resin.*—This extract, on heating with dilute sulphuric acid, yielded formic, butyric, and other acids, together with sugar.

(*b*) *Chloroform Extract of the Hydrolyzed Resin.*—This extract, like the preceding one, yielded small amounts of formic, butyric, and other acids, together with sugar.

(*c*) *Ethyl Acetate Extract of the Hydrolyzed Resin.*—This extract, on heating with dilute sulphuric acid, yielded formic, butyric, *d*-methylethylacetic, and other acids, together with sugar.

(*d*) *Alcohol Extract of the Hydrolyzed Resin.*—This extract could be obtained in the form of a nearly colorless powder, which melted at 110–115°, and had $(\alpha)_D - 33.53°$. When heated with dilute sulphuric acid it yielded, in addition to sugar, small amounts of formic, butyric, and valeric acids, together with convolvulinolic and ipurolic acids. The last mentioned acid possesses the formula $C_{13}H_{25}(OH)_2 \cdot CO_2H$, and was first obtained by the authors from the stems of Ipomœa purpurea, Roth.[1]

By the oxidation of this extract with nitric acid, azelaic and sebacic acids were obtained.

Each of the above-described extracts of the hydrolyzed resin appeared to be only partly glucosidic, and to contain a readily soluble organic acid which was unaffected by the treatment with dilute sulphuric acid.

Scammony

The gum-resin, obtained by incision of the horny root, is commonly designated as scammony or virgin scammony. Its value as a purgative agent depends on its resinous constituent, which is now generally obtained

[1] Am. J. Pharm., 80, 273 (1908).

by extracting the dried root with a suitable solvent and washing the resinous mass with water until it comes away clear. The resin obtained by this means is almost completely soluble in ether, and the ether soluble portion has been termed "scammonin," being synonymous with the "jalapin" or ether soluble portion of jalap resin.

Scammony resin is not used as largely as jalap, but it will be found in cathartic pills and tablets combined usually with colocynth, and containing in addition Podophyllum, soap, aloes, cardamom, and potassium sulphate. It is one of the ingredients of powdered extract colocynth compound, and as this product enters into the composition of a large variety of formulas the presence of small quantities of scammony may be expected whenever colocynth is discovered.

Power and Rogerson [1] examined the root of Convolvulus scammonia, and found it to contain about 10 per cent of resins. They also identified sucrose, scopoletin, melting 203–204°, giving a beautiful blue fluorescence with alkalies, and 3–4 dihydroxycumaric acid. The resin which they obtained by alcoholic extraction was soluble to the extent of 90–95 per cent in ether, and thus differed markedly from the resin of jalap. Its rotation in absolute alcohol was $(\alpha)_D - 19.87°$. It has a peculiar and characteristic odor which is brought out on warming or by rubbing in a mortar. The resin yielded a phytosterol, melting 135–136°, soluble in petroleum ether, compounds of palmitic and stearic acid, ipuranol, $C_{33}H_{56}O_6$, and on hydrolyzing with barium hydroxide, *d*-α-methyl butyric, tiglic, formic, and valeric acids, methyl jalapinolate, melting 47–49°, and jalapinolic acid, melting 67–68°, a mixture of sugars, and indefinite bodies. Ipuranol appears to be a phytosterol glucoside which on hydrolysis with aqueous hydrochloric acid is resolved into a phytosterol, $C_{27}H_{46}O_{12}$, and glucose.

The same authors examined virgin scammony and found it to be soluble to the extent of 80–85 per cent in ether, and to contain in addition to the substance mentioned above, small amounts of hentriacontane $C_{31}H_{64}$, and cetyl alcohol.

The saponification number of the resin runs from 230–240 (Taylor) or 263 (Cowie).

Scammony resin is adulterated with rosin, chalk, starch, resinous material and extractives from other drugs and Dieterich reports a case of adulteration with lead sulphide.

Mexican Scammony

The root of I. orizabensis is known under various names, such as Light, Fusiform, or Woody Jalap, or Orizaba Root (see Holmes, Pharm. J., 1904, 72, 326).

[1] Chem. Soc. Trans., 101, 1912, 398.

It contains about 15 per cent of crude resin, of which from 70–75 per cent is soluble in ether.

Power and Rogersons' [1] investigation of this drug may be summarized as follows:

From the portion of the extract which was soluble in water, the following compounds were isolated: (1) scopoletin, $C_{10}H_8O_4$ (m.p. 203–204°), a small proportion of which appeared to be present in the form of a glucoside; (2) 3 : 4 dihydroxycinnamic acid, $C_9H_8O_4$ (m.p. 223–225°), from which the methyl ester (m.p. 158–160°) was prepared. The aqueous liquid contained, furthermore, a quantity of sugar, which yielded *d*-phenylglucosazone (m.p. 205–206°).

The portion of the alcoholic extract which was insoluble in water consisted of a resin which possessed the above-mentioned characteristics. The resin was first successively extracted with various solvents, and the resulting extracts were then further examined.

I. **Petroleum Extract of the Resin.**—From this extract the following substances were obtained: (1) hentriacontane, $C_{31}H_{64}$; (2) a phytosterol, $C_{27}H_{46}O$; (3) cetyl alcohol, $C_{16}H_{34}O$; (4) a mixture of fatty acids, consisting of palmitic, stearic, oleic, and linolenic acids.

II. **Ethereal Extract of the Resin.**—The optical rotatory power of this extract was $(\alpha)_D - 20.5°$. After hydrolysis with barium hydroxide it yielded: (1) ipuranol, $C_{23}H_{38}O_2(OH)_2$; (2) *d*-α-methylbutyric acid; (3) tiglic acid; and a product which on acid hydrolysis, gave (4) jalapinolic acid, $C_{15}H_{30}(OH)\cdot CO_2H$ (m.p. 67–68°); $(\alpha)_D + 0.79°$), together with a little methyl jalapinolate, and (5) a mixture of sugars, consisting of dextrose and a methylpentose. The latter yielded an osazone melting at 180–182° and a tetra-acetyl derivative, $C_6H_8O_5(CO\cdot CH_3)_4$, which apparently is a new compound. This derivative crystallizes in handsome, prismatic needles, melting at 142–143°, and has $(\alpha)_D + 21.64°$. The ethyl acetate extract of the product resulting from the alkaline hydrolysis of the ethereal extract of the resin gave on oxidation with nitric acid a mixture of acids, consisting apparently of optically active valeric and hexoic acids, together with sebacic and *n*-nonanedicarboxylic acids.

III. **Chloroform Extract of the Resin.**—This was relatively small in amount, and consisted of a dark resinous product.

IV. **Ethyl Acetate Extract of the Resin.**—The optical rotatory power of this extract was $(\alpha)_D - 28.01°$. After hydrolysis with barium hydroxide it yielded products from which the same substances were obtained as from the ethereal extract of the resin, with the exception of the small amount of ipuranol.

V. **Alcohol Extract of the Resin.**—This was a black, amorphous product of a glucosidic nature, but which yielded nothing definite on hydrolysis.

[1] Chem. Soc. Trans., 1912, 101, 1.

It may also be noted that the portion of the resin which is soluble in ether is not identical with the ether-soluble portion of jalap resin.

It has a saponification value of about 186–188 (Taylor) 295-327 (Cowie).

While there are some minor differences between the composition of the resin of this root and that of C. scammonia thus far ascertained, it is apparent that the resins could readily be substituted for each other with little chance of certain detection and as will probably be demonstrated, they are equally valuable for medicinal purposes.

IPOMOEA TURPETHUM

The root of I. turpethum, an East Indian species, yields a gum resin similar to jalap resin in its properties. This resin is called Turpeth and is used medicinally. Reports of its composition have appeared, but they require confirmation and further research. It is soluble in alcohol but insoluble in ether.

Dieterich reports the following constants: acid value 20.55–24.45; ester value 137.27–141.01; saponification value hot 160.49–163.94.

Examination of Resins.—In order to test these resins for adulterants a few simple determinations should be made and the results compared with those obtained with authentic specimens.

Cowie recommends the following tests for Jalap resin, the same procedure being applicable to the others: 1. Moisture. 2. Ash. 3. Solubility in ether, obtained by rubbing the sample in a mortar with ether, filtering and evaporating the solvent in a tared dish. 4. Acid value, obtained by dissolving in alcohol and titrating. 5. Saponification value. One hour's boiling with N/2 alcoholic potash and titration with N/2 hydrochloric acid. 6. Absence of colopheny, .25 gram in 5 mils acetic anhydride should give no purple color with 2 drops of strong sulphuric acid. 7. Absence of guaiacum, no greenish-blue color with ferric chloride. 8. Treatment with water results in no water soluble substance nor any starch reaction.

Cowie's results obtained by applying these tests to authentic resins yielded the following data:

	Moisture, Per Cent.	Ash, Per cent.	Ether Soluble, Per cent.	Acid Value.	Sapon. Value.
Brown Jalap resin.....	5–5.6	0.3	10	11.2–14	333–338
Cowie White Jalap resin..	3–3.1	0.02	0.3	2.8	417
White Scammony resin...	2.52–5.3	0.02	100.0	2.8	241
Brown Scammony resin...	4.5–5.1	.15	95	25.2–28	263
Mexican Scammony resin.	2–3.05	.16–.20	68.6–72	8.4	295–327

Taylor's[1] results below with true and Mexican Scammony resins do not agree with Cowie's, but the differences may be due to the methods of analysis. Taylor dilutes with water before titrating with acid to determine the saponification value.

	Moisture, Per Cent.	Ash, Per Cent.	Ether Soluble, Per Cent.	Acid Value.	Sapon. Value.
True Scammony....	1.65–1.86	.05–.20	99–99.7	15.6–21.3	238–240
Mexican Scammony.	1.77–2.03	.09–.22	96.5–99.6	15.5–21.5	186.6–187

Evans Sons, Lescher, and Webb consider that the ester value of the resin is the most important factor in differentiating the source. They report the following data:

	Acid Value.	Sapon. Value.	Ester Value.	Iodine Number.
Jalap.....	8.4–26	144.8–185	121.8–162	9–24.2
Virgin Scammony...	7–12	240–250	233–242.7	3.6–9.6
Mexican Scammony.	11.2–24.1	172.5–202.7	161.3–178.6	8.3–15.3

Boudier[2] states that pure scammony resin should not give an acid number above 21 nor a saponification value below 235.

Weigel[3] gives Asiatic scammony resin an acid number from 14–28, a saponification value 179–228; and Mexican Scammony 14.6 and 180–185. Jalap resin, acid number 12.6–16.8, saponification value 162–185. He considers that the acid value has greater significance than the saponification value.

It has been suggested that the specific rotatory power might aid in detecting adulterants in, and discriminating between these resins. The resin obtained by extracting scammony root with a solvent has a rotation varying from $-18°\ 30'$ to $-23°\ 30'$ and the upper limit for the resin from the natural scammony is $-25°$. Mexican scammony rotates from $-23°\ 30'$ to $-25°$. The rotation of jalap resin is $-36°$ to $-37°$, that of I. turpethum is high and that of I. purpurea -50 to $-95°$. The addition of colophony, sandarac, or mastic would lower the rotatory power, as their direction is dextro.

It is apparent from the preceding review of the resins of the Convolvulaceæ that their absolute identity in complex mixtures with other drugs is a matter of considerable difficulty. They are usually accompanied by other resinous drugs, and, while as a rule a mixture containing jalap will

[1] Am. J. Pharm., 1909, 81, 105.
[1] J. Pharm. Chem., 5, 97 and 154.
[3] Pharm. Zentralhalle, 51, 721.

not contain scammony, jalap preparations often include extract of colocynth compound which has a little scammony in its make up.

In the general scheme of analysis the resins will be extracted from the sample by alcohol, and, on driving off the solvent and treating the residue with water, they will be left behind in the dish. If this resinous mass is completely soluble in ether, the absence of jalap is established, but not necessarily the absence of the commercial "jalapin." If a residue is left undissolved, it may be freed from ether by warming and a portion treated with concentrated sulphuric acid, which will produce a brown to blood-red with a noticeable jalap-like odor if the drug is present. The balance of the residue is treated with chloroform and filtered, the chloroform solution shaken with sodium carbonate, which will show a marked blue fluorescence due to β-methylæsculetin. This reaction can be rendered more certain by drawing off the alkaline solution, acidulating, filtering, and shaking with ether, discarding the acid liquid, and finally shaking the ethereal solution with ammonia, when a fine blue fluorescence will be obtained. A similar reaction will be obtained if Gelsemium is present in a mixture, but this drug can be readily distinguished from jalap by its characteristic alkaloids.

That portion of the resinous matter which is soluble in ether will contain scammony and on evaporating the solvent and warming the residue with sodium carbonate solution it will not entirely dissolve, and the insoluble portion after washing and drying will swell up to a yellow mass with nitric acid.

There are no methods for the accurate quantitative determination of resins or for separating one from the other. It is easy to determine the total amount of resinous matter in a drug mixture, but as nearly every vegetable drug contains some material of this nature, and as jalap and scammony are usually combined with other drugs, any estimate of resin will under such conditions be of little value.

CHAPTER XII

MISCELLANEOUS ACTING DRUGS

SANTONIN AND PRINCIPLES OF THE ARTEMISIAS AND CERTAIN ALLIED DRUGS

The genus Artemisia of the tribe Anthemideæ (Compositæ) embraces over two hundred species, some of which are of value as medicinal agents. The flowering tops of A. cina, A. maritima, A. gallica, and perhaps others contain santonin, a substance of peculiar lactone-like composition which has a specific action on ascarides and lumbricoids. On this account santonin has become an important remedy for the expulsion of worms, and the ground drug, called Santonica (the true Levant wormseed), is extensively employed in stock remedies.

It is evident that a great deal of Santonica is devoid of santonin, and that the drug as imported into the country may contain anywhere from 3.5 per cent to nothing. It is not unlikely that the flowering tops of other species of Artemisia are shipped indiscriminately for Santonica.

A. absinthium is the well-known wormwood, which is supposed to be one of the ingredients of absinthe. This species, as well as half a dozen others growing in this country, are employed as bitter tonics and stomachics and sometimes as emmenagogues, antiperiodics, diuretics, anthelmintics, etc. Nearly all of the Artemisias growing in North America are called wormwood, hence it would not be surprising if twenty or more different species were collected and marketed. A. absinthium contains thujone and absinthiin, the former a volatile ketone which gives a characteristic property to the oil of wormwood, and the latter a bitter principle, perhaps of glucosidal nature. Of the other species we may mention A. abrotanum, southernwood, A. frigida, wild or mountain sage, A. pontica, Roman wormwood (which must not be confused with Ambrosia artemisiæfolia), A. vulgaris, mugwort or motherwort, and A. mertellina, silky wormwood from the Alps and Central Europe.

A. absinthium is the only one whose composition has received any attention, and the chemistry of that is in need of revision and amplification. While it is supposed to be used in the manufacture of the liqueur "Absinthe," and the deleterious properties of the drink credited to its presence, it is doubtful if a careful and sane investigation would sustain these convictions. The writer had occasion at one time to investigate samples

of all of the brands of Absinthe then being imported, as well as some of those made in this country, and as a result it appeared that in but one case was there any suggestion of a bitter principle resembling absinthiin, and the amount of thujone and oil of wormwood was in too small amount to yield any characteristic reaction. However, the ban was placed on imported "Absinthe" because it was deleterious to the health of the people of the United States, which it probably was because of its alcohol content, in the same way that all imported whiskies, wines, and champagnes might be considered deleterious.

Allusion was made above to Ambrosia artemisiæfolia syn., A. elatior, which belongs to another family, the Ambrosiacea. This is the well-known Roman wormwood or ragweed of waste places and cultivated fields, and which is credited with being one of the aggravating causes of hay fever. Its extract has been recommended as a remedy for asthmatic conditions. A serum called Pollantin is prepared from the "serum toxin" of ragweed and is used locally in hay fever.

There is another drug, Chenopodium or American wormseed, which can be considered to advantage with this group, both because of its use and the character of its active principle. The drug American wormseed is the fruit of Chenopodium ambrosioides (Chenopodiaceæ, Goosefoot family) (Syn. C. anthelminticum). The fruit and oil distilled therefrom are official in the Pharmacopœia. An extract of the drug is used in the preparation of combination worm remedies and laxatives for children and the oil, which consists largely of ascaridol, is a valuable vermifuge.

To sum up the pharmacognosy of these paragraphs:

Artemisia maritima and A. cina	Levant wormseed:	Santonica
A. absinthium	Wormwood	Absinthe
A. pontica	Roman Wormwood	(Not the common Roman wormwood of waste places and fields.)
Ambrosia elatior syn. artemisiafolia.	Roman wormwood	Ragweed
Chenopodium ambrosioides syn. anthelminticum	American Wormseed	

SANTONICA

Santonica is used in the preparation of condition powders for stock. Its anthelmintic principle, santonin, is a popular remedy and is dispensed in tablet or lozenge form either by itself or in combination with calomel or podophyllin or both.

The amount of santonin varies with the age of the bud and the individual plant. It is supposed to be greatest just before the expansion of the flowers. For its determination in the drug the analyst is referred to page 64.

Santonin, $C_{15}H_{18}O_3$, crystallizes from dilute alcohol in pearly crystals, melting 171–172°. When dissolved in chloroform, the solvent on evaporation leaves a colorless syrup which crystallizes in feathery, frostlike radiating groups. When cautiously heated, santonin may be sublimed, but there is no danger of loss from drying at 100°. It gradually turns yellow on exposure to sunlight.

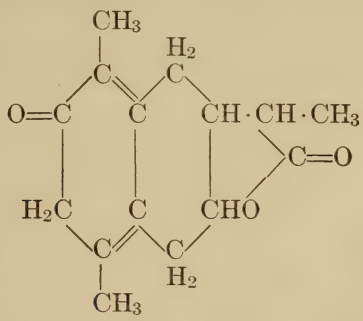
Santonin is only slightly soluble in cold water, but is somewhat more soluble in boiling water. It is fairly soluble in cold alcohol and ether and with ease in chloroform and boiling alcohol. It can be completely removed from an acid mixture by means of chloroform, but it is not removable by alkalies from its solution in organic solvents. It dissolves in alkalies, but the solution cannot be titrated to determine the santonin.

Santonin is strongly lævorotatory. $(\alpha)_D - 173.8$ for alcohol and -171.4 for chloroform. It is neutral to litmus.

Solutions of santonin are not precipitated by ordinary alkaloidal precipitants, but the solid substance gives a few characteristic color tests. It dissolves in concentrated sulphuric acid with a yellow color, the isolated crystals being surrounded with a violet ring, as they join the solution; if this solution is then diluted with an equal volume of water and treated with ferric chloride a violet color is produced. Nitric acid produces no characteristic reaction, but on evaporating and adding alcoholic potash an intense orange color results. Santonin itself gives a red color with alcoholic potash.

Santonin has the property of affecting the vision to such an extent tnat everything appears yellow.

Santonin is the lactone of santoninic acid, $C_{15}H_{20}O_4$, a derivative of naphthalene. The constitution of the lactone is probably



Santoninic acid may be obtained by treating santonin with alkalies, and after solution has taken place an excess of hydrochloric acid is added and the acid immediately shaken out with ether. It reverts to santonin if allowed to stand in contact with mineral acid, or when warmed to 120°. It crystallizes in rhombic crystals from alcohol and has an acid reaction.

Santonic acid, an isomer and much more stable than santoninic acid, is prepared by boiling santonin twelve hours with barium hydrate solution, acidifying with hydrochloric acid, and shaking out with ether. It forms rhombic crystals, melting 163°.

Artemisin or oxysantonin, melting 202°, accompanies santonin in the drug.

In analytical work it is not difficult to distinguish santonin from the other principles present in medicinal compounds. It is very sparingly soluble in acid aqueous solutions and may be separated from acid mixture with ease by chloroform. It is soluble in alcohol and crystallizes from dilute alcohol, melting 171–172°. Its color reactions are characteristic, and it gives negative tests with most of the reagents used for distinguishing the alkaloids and other commonly occuring substances.

Determination of Santonin in Tablets.—Transfer 8 tablets to a small Squibb separator, and moisten with water (5 mils); add 2 drops dilute sulphuric acid. Shake out three times with 25-mil portions of chloroform, collecting each shake-out in another separator. Wash the combined chloroformic solutions with 5 mils of water, and when the water has entirely risen to the surface and no minute bubbles are seen through the mass of the liquid, run the chloroform into a tared beaker, through a pledget of absorbent cotton in the stem of the funnel. Evaporate the chloroform over the water-bath, using a fan, and when solvent has evaporated, dry for fifteen minutes in water oven. Weigh directly as santonin.

With calomel present, the above procedure is not satisfactory, owing to the emulsification which takes place when calomel, chloroform, and water are shaken together. The determination should be conducted in a 25-mil graduated cylinder with lip. Introduce 8 tablets and crush with a stout stirring rod. Add 20 mils chloroform and stir mixture with the rod. Filter the chloroform through a good grade of dry paper, free from pinholes, into a tared beaker. Repeat twice, then evaporate chloroform and finish determination as above.

Calomel is insoluble in dry neutral chloroform.

ABSINTHIIN AND ARTEMISIA

Artemisia absinthium is used as a tonic and stomachic and it will sometimes be found in liniments mixed with menthol, oils of sassafras, calendula, and Echinacea angustifolia.

Absinthiin is the bitter principle. It appears to be a glucoside, but its chemistry needs further study. The purified substance has been described as consisting of white inodorous crystals having the composition $C_{15}H_{20}O_4$, and melting 68°. It is reported as yielding dextrose on acid hydrolysis, and phloroglucinol when heated with alkali hydroxides.

The chemist should not depend on this meager description for the

characteristics of the bitter principle of wormwood. An extract of the true drug will always contain thujone, which lends itself much easier to detection, and whose properties are now well known. An acid aqueous solution obtained by digesting an evaporated alcoholic solution of wormwood with water and acidulating, will yield a vitreous bitter residue to petroleum ether and to ether. Probably both of these residues contain absinthiin.

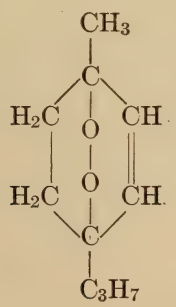
If the chemist suspects the presence of this drug, a portion of the same should be distilled with steam and the distillate examined for thujone, while the residue is evaporated to dryness, extracted with alcohol, the alcoholic solution separated and evaporated and the residue taken up with warm water which is then acidulated and shaken out with petroleum ether and with ether. If there is any appreciable quantity of the drug present in a medicinal compound it is recognizable by its odor, provided this is not masked by the aroma of high-scented flavoring oils.

The test for thujone with sodium nitroprusside and acetic acid is of course a general reaction for ketones and ought not to be conclusive. Many other oils have been found to give the same reaction with sodium nitroprusside as oil of wormwood, namely, hyssop, calamus, verbena, and savine.

ASCARIDOLE AND AMERICAN WORMSEED

The drug known as American Wormseed consists of the fruit of Chenopodium ambrosioides syn. anthelminticum. Its extract is employed as a worm remedy and is dispensed with extract of senna, Cascara sagrada, pumpkin seed, Rochelle salt and sodium bicarbonate in a class of medicines of the " Castoria " type, which are recommended as laxatives and worm expellants especially for children. The oil of Chenopodium is official in the Pharmacopœia and consists of about 70 per cent of ascaridole, which seems to be the anthelmintic principle. Ascaridole will of course be found in the fluid extract.

Ascaridole is an organic peroxide which has been assigned by Wallach the constitution



It boils 96–97° under 8 mm. Specific gravity .9985 at 20° C. n_D at 20° −1.4769, sometimes slightly lævorotatory, probably due to impurity. It is explosive when heated or when treated with concentrated mineral acids. On shaking with nearly saturated ferrous sulphate at a temperature below 30°, a viscous product, ascaridol glycol, is obtained, which boils 271–272°. If the reaction is allowed to proceed without cooling, basic ferric sulphate will be precipitated and a combustible gas evolved.

Ascaridole will not react with the reagents used to characterize the alcohols, ethers, ketones, aldehydes, and acids, but it is soluble in the ordinary organic solvents, and though it is present in the children's remedies in small quantity, its indifference to reagents will allow of its separation from other ingredients to such an extent that tests for its explosiveness can be applied.

RAGWEED OR ROMAN WORMWOOD

There are as yet no published data on the chemistry of Ambrosia elatior. The alcoholic extract has been used in conjunction with extract of Solidago species (golden rod) as a remedy for hay fever and asthma, but its application in this way is limited.

Of late years it has been suggested that the plant gives off an albumen which has a toxic action on the mucous membrane. Based on this theory a serum has been prepared which when applied locally is stated to be of value in alleviating hay fever.

Pollantin, Fall—Dunbar's Serum.—Antitoxic serum from horses treated with pollen toxin derived from ragweed.

Horses are injected with gradually increased doses of pollen toxin (derived from ragweed), which results in the formation of an antitoxin after two or three months of treatment. The horses are then bled and the strength of the serum is estimated by determining the proportion which will prevent the action of a solution of pollen toxin, of which one drop is barely sufficient to produce a reaction when instilled into the conjunctival sac of a hay-fever patient. The serum is preserved by the addition of 0.25 per cent of phenol.

It is a clear, slightly yellowish liquid, having the odor and taste of a dilute solution of phenol. On standing, the liquid deposits a slight precipitate. The liquid is alkaline in reaction and not irritating to the normal conjunctiva.

Pollantin, Fall, has no pharmacologic action except the neutralization of the pollen toxin. The serum is not intended for use hypodermically. It is employed for the relief of hay fever and it seems to be effective in a proportion of cases. It may be used as a prophylactic.

Pollantin Powder, Fall.—A powder obtained by evaporating, *in vacuo*,

pollantin serum derived from ragweed toxin at about 45° C., and mixing it with sterilized sugar of milk.

It is a fine, slightly yellowish, almost odorless powder, almost but not entirely soluble in water, and having a slight alkaline reaction. The tests are the same as for the liquid. It should reduce Fehling's solution.

The powder is applied to the eyes by dusting on the conjunctiva and to the nose by snuffing into one nostril, the other being closed, a piece as large as a lentil.

ASPIDIUM

The official drug called Malefern consists of the rhizome of Dryopteris Filix-mas syn. Aspidium Filix-mas (Polypodiaceæ), true malefern, or of D. marginalis, evergreen wood-fern or marginal shield fern.

The extract of this drug, or more commonly its oleoresin, is used in the removal of tape worm, and is usually administered with castor oil and kamala.

Malefern oleoresin is often adulterated with castor oil. This product, which is also known as liquid extract of malefern, is of an oily consistency, obtained by an ether extraction of the drug. It has a specific gravity of 1.018–1.052, refractive index 1.4995–1.5157, saponification value 227–259, unsaponifiable matter 4 to 7 per cent, material insoluble in petroleum ether 3 to 15 per cent, crude filicin 19 to 28 per cent, as determined by the method of the Swiss Pharmacopœia. The potash extract of oleoresin malefern is that portion of an ether solution of 20 grams soluble in 1 per cent potassium hydroxide. It contains acid constituents. The potash insoluble is that which remains in the ether and in genuine samples it amounts to about 50 per cent. The acid number of the potash insoluble portion is 28 to 36 in genuine samples but runs up as high as 149 if castor oil is present.

The Swiss method is as follows:

Five grams of the extract are transferred to a 200-mil flask, 30 grams of ether added, followed by 100 grams of 3 per cent barium hydroxide, the whole well shaken, transferred to a separatory funnel, and allowed to stand ten minutes. The aqueous portion is filtered, 86 grams of the filtrate treated with 3 mils of hydrochloric acid, or sufficient to render it acid, and then shaken with 30–20–15 mil portions of ether. The combined ether extracts are filtered, the filter washed with ether, and the solvent solution evaporated in a tared dish, drying to constant weight at 100° C. The residue should weigh 1.04 to 1.12 grams, corresponding to 26–28 per cent crude filicin in the extract.

FILICIC ACID AND RELATED SUBSTANCES

The most recent work indicates that Aspidium probably contains the following constituents, in approximately the amount indicated: Filicic acid, 3.5 per cent; flavaspidic acid, 2.5 per cent; albaspidin, 0.05 per cent; aspidinol, 0.10 per cent; flavaspidin, 0.10 per cent; amorphous acid, 5.0 per cent and filicic nigrine, 6.0 per cent. These substances are, for the greater part, derivatives of phloroglucinol, and some of them are ketones possessing acid characters.

The various formulas assigned to the filicic acids and the different results reported regarding their physiological activity have given rise to much confusion, leaving the chemistry in an unsettled condition. One of the first formulas assigned to filicic acid is that of Luck—$C_{26}H_{30}O_9$, which differs considerably from the formula $C_{14}H_{18}O_5$—given this substance by Grabowski, and $C_{14}H_{16}O_5$, as suggested by Daccoma. Later two forms, a crystalline and an amorphous filicic acid, were recognized by Poulson, who suggested the formula, $C_{36}H_{40}O_{12}$, for the crystalline filicic acid and $C_{36}H_{42}O_{13}$ for the amorphous acid, which later he considered as the active therapeutic principle of aspidium. Poulson believed the crystalline acid to be the anydride of the amorphous acid. More recently, Gallas has stated the formula for both the crystalline and the amorphous filicic acid to be $C_{18}H_{22}O_6$. Gallas and later Kraft concluded that one form of the acid was the lactone of the other form. Filicinic acid, which has the formula $C_8H_{16}O_3$, is sometimes confused with filicic acid. Besides a difference in the theories regarding the constitution of the various filicic acids, there has been considerable controversy over the anthelmintic properties of these substances.

Amorphous filicic acid is an organic acid, $C_{36}H_{42}O_{13}$, obtained from several species of Aspidium. It is a white or yellow powder, without odor or taste, melting at 125° C., soluble in cold alcohol.

Amorphous filicic acid has been recommended as an anthelmintic, and is generally considered one of the active principles of several species of Aspidium. It is usually combined with calomel and jalap.

The crystalline filicic acid, also designated as filicinic acid, which is considered as an anhydride of the amorphous filicic acid, is devoid of anthelmintic action.

Filmaron, $C_{47}H_{54}O_{16}$, is an active anthelmintic constituent obtained from the ethereal extract of Aspidium. It has acid properties and occurs as a straw-colored amorphous powder, insoluble in water, difficultly soluble in ethyl and methyl alcohols and rather difficultly soluble in petroleum ether. It is readily soluble in all proportions of ether, acetic ether, amyl alcohol, chloroform, benzin, carbon disulphide, and acetone, and also, though with partial decomposition, in solutions of the alkalies

and alkali carbonates. The alcoholic solution exhibits a slightly acid reaction. Filmaron melts at about 60° C. It exhibits a strong tendency to cake together to form a resinous mass, which is difficult to reduce to powder and dispense; hence it is not marketed in substance, but as a 10 per cent castor oil solution, which is known as " Filmaron oil."

Five-tenths gram filmaron and 5 gram pumice stone, and 1 gram magnesia are finely triturated with 250 mils water, the mixture shaken for half an hour, and then filtered. On passing a rapid current of carbon dioxide through the filtrate a voluminous, flocculent precipitate forms; the filtrate should afford but very slight precipitate on the addition of hydrochloric acid.

On dissolving 0.1 gram filmaron in 0.2 gram acetic ether or 0.2 gram carbon disulphide by rotation in a test-tube, and setting the stoppered tube aside for three days, no separation should have taken place at the end of this time (absence of other malefern constituents, filicic acid and flavaspidic acid).

One-tenth gram filmaron should completely dissolve in 0.5 gram warm petroleum ether and leave no more than a slight trace of undissolved substance. To detect the filmaron in the castor oil solution (filmaron oil), dilute the filmaron oil with ether, shake out with sodium hydroxide solution, acidulate the alkaline liquid, and then take up the liberated filmaron with ether. On evaporating the ether and filmaron is obtained as a residue.

PICROTOXIN

The berries of Cocculus indicus or Anamirata paniculata (Menispermaceæ), a small climbing shrub growing in India and the Malay Archipelago, contain a feebly acid principle, picrotoxin. Both the berries and purified picrotoxin are used medicinally in nervous disorders, where they exert a sedative action, and in phthisis to relieve night sweats. They are also employed externally to destroy parasites. Pills and hypodermic tablets of picrotoxin usually contain about $\frac{1}{60}$ to $\frac{1}{50}$ grain. A decoction of the berries acts as a powerful fish poison and the fruit has received the name " fish berry." The practice of collecting fish by means of the fruit is not uncommon, and there are certain proprietary poisons which owe their efficacy to the presence of picrotoxin.

The kernel contains the picrotoxin with picrotin and picrotoxinin. The shells contain alkaloidal substances to which the names menispermin and paramenispermin have been given.

PICROTOXIN, $C_{30}H_{34}O_{13}$

Picrotoxin, when pure, is a colorless, shiny, prismatic crystalline substance, bitter, odorless, permanent in the air, and melting at 200° C.

It is sparingly soluble in cold water, but dissolves quite easily in hot aqueous solutions and in the presence of acids or alkalies. It dissolves easily in hot alcohol and benzol and less readily in chloroform and ether, and it may be removed from acid solutions by any of these immiscible solvents, but it cannot be extracted in the presence of alkalies.

Treated with concentrated sulphuric acid, picrotoxin gives a yellow color, turning orange and becoming red on warming and gradually reddish-brown, while the solution becomes fluorescent, best observed by pouring the liquid into a narrow test-tube. A drop of a 20 per cent alcoholic solution of anisaldehyde added to a solution of picrotoxin in sulphuric acid produces a blue-violet ring, becoming blue. Evaporated with concentrated nitric acid it leaves a reddish-yellow residue, which becomes red when moistened with aqueous alkali hydroxide. A solution in concentrated sulphuric acid treated with potassium nitrate, gives a red to violet color when strong alkali hydroxide is added. A mixture of picrotoxin and sucrose becomes red on treatment with concentrated sulphuric acid.

An aqueous solution of picrotoxin reduces Fehling's solution and ammoniacal silver oxide, but it gives no precipitate with neutral, or basic lead acetate, Mayer's reagent, gold, platinic, or mercuric chlorides, tannic acid, or most other general reagents for alkaloids.

Picrotoxin is not a glucoside. It is decomposed by the action of hydrochloric acid into picrotin and picrotoxinin, both dilactones:

$$C_{30}H_{34}O_{13} = \underset{\text{Picrotin}}{C_{15}H_{18}O_7} + \underset{\text{Picrotoxinin}}{C_{15}H_{16}O_6}$$

The reaction also occurs when a solution in chloroform is allowed to stand, or when an aqueous or benzene solution is boiled. Both of the products of decomposition reduce Fehling's solution and ammoniacal silver oxide. Picrotin melts 245–250° and picrotoxinin at 200 C.

Hydrolysis with aqueous alkali first gives alpha-picrotoxininic acid, $C_{15}H_{18}O_7$, and beta-picrotinic acid, $C_{15}H_{22}O_9$. These yield with excess alkali the dicarboxylic acids of picrotoxinin and picrotin, $C_{15}H_{20}O_8$ and $C_{15}H_{22}O_9$, respectively. These bodies, with the exception of alpha-picrotoxininic acid, do not reduce Fehling's solution or ammoniacal silver oxide.

Picrotoxin is speedily decomposed when boiled with alkalies.

The separation of picrotoxin from medicinal preparations is not difficult. In the general scheme of analysis it will be found in greatest amount in the fraction obtained by shaking an acid aqueous solution with chloroform. It may be purified by dissolving in dilute ammonia, shaking out neutral substances with ether and chloroform, acidulating, and extracting with chloroform. The crystalline residue is then subjected to

the several color reactions, and a dilute aqueous solution may be added to a bowl containing a few small fish. The fish will soon begin to swim with uncertainty, lose their balance and ultimately rise to the surface, lying on their sides and frequently opening mouths and gill covers.

Its estimation in pills and tablets may be accomplished by transferring a sufficient quantity of the sample to a separatory funnel, disintegrating with water, acidulating, and agitating with chloroform. Three or four extractions should be made and the combined extracts filtered into a tared beaker, evaporated, and weighed.

CASPSICUM AND CAPSAICIN

Capsaicin is the pungent principle of the fruit of Capsicum fastigiatum (Solanaceæ), C. annuum, and other species of Capsicum, the former being by far the most pungent and furnishing the cayenne type of red pepper, to which medicinal Capsicum belongs, while the latter provides the paprika.

Capsicum is administered both in the powdered form and as the oleoresin in cases of enfeebled or languid digestion, dyspepsia, atonic gout, and colic, and externally as a rubefacient. It will be found in some liniment formulas, also in ointments and plasters and to a large extent in pills and tablets. It is also used to increase the pungency of ginger ales and a few other types of temperance beverages.

Capsicum and myrrh are dispensed together in liquid form, and compound tincture of opium and chlorodyne formulas contain Capsicum. Among the great number of different pill and tablet combinations the following types may be mentioned, all of which often contain Capsicum; aloin, belladonna, strychnin, and Podophyllum resin; belladonna, Hyoscyamus, Nux Vomica and Podophyllum resin; aloin, Nux Vomica, Podophyllum resin, colocynth comp. and croton oil; aloin, jalap resin, Podophyllum resin; strychnin and Hyoscyamus; aloes, gamboge, Podophyllum resin, and croton oil; aloin, jalap, and Podophyllum resin; gamboge, leptandra, Hyoscyamus, and oil of peppermint; belladonna, Nux Vomica, Cascara sagrada, Euonymus and Xanthoxylon; Podophyllum resin, Taraxacum, Euonymus, Eupatorium, and Apocynum; Podophyllum resin, Hyoscyamus, Nux Vomica and mercury mass; the above formulas being of the cathartic type.

Mixtures intended as liver regulators will contain jalap and Podophyllum resins, Hyoscyamus and colocynth comp.; aloes, rhubarb, Podophyllum resin, and Hyoscyamus; Podophyllum resin, Nux Vomica, Leptandra, and Iris versicolor; jalap, and Podophyllum resin, Leptandra and gamboge; aloes, jalap, gamboge, Leptandra, Veratrum viride, croton oil, and calomel, sometimes with addition of Podophyllum and butternut. Stomachics and anti-dyspeptic tablets and pills will contain rhu-

barb, Cinchona and Ignatia; rhubarb, strychnin, and ipecac; pepsin, Nux Vomica, and ipecac; pepsin, Nux Vomica, and charcoal; rhubarb, strychnin, ipecac, gentian, and sodium bicarbonate; gentian, mercury mass, ipecac, and strychnin; ginger, sodium salicylate, and cardamom; strychnin, ipecac, pepper, and gentian. Compounds intended for the relief of diarrhea and summer cholera consist of rhubarb, opium, camphor, and oil of peppermint; calomel, ipecac, morphin, and camphor; morphin, Cannabis sativa, nitroglycerin, Hyoscyamus, and oil of peppermint. Compounds for ague contain Gelsemium, Xanthoxylon, and cinchonidin; Nux Vomica, Hyoscyamus, and quinin; arsenous acid, cinchona alkaloids, eucalyptus, and iron ferrocyanide. Antiperiodic pills contain cinchonidin, ferrous sulphate, Podophyllum resin, strychnin, and Gelsemium. Cold tablets consist of quinin, aloin, calomel, aconite, ipecac, and opium; quinin, aloin, sodium bromide, acetanilid, and Cascara sagrada; and a formula for dipsomania contains quinin, arsenous acid, strychnin, and zinc oxide.

The Capsicum species were originally confined to the American tropics, but they are now cultivated in all parts of the world.

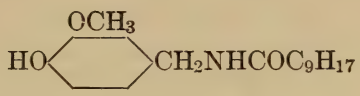
The characteristic constituent is a pungent substance, capsaicin, which is present to the amount of about .15 per cent. The drug also contains a small quantity of a non-pungent alkaloidal substance. Considerable oily material can be extracted by volatile solvents, and oleoresin of capsicum, which contains practically all of the capsaicin, is a well-known pharmaceutical product and is the form in which the drug is usually administered.

Capsaicin crystallizes in pearly white leaflets melting 64 to 64.5°, but as ordinarily extracted in analytical work it is a colorless amorphous residue, often in such small quantity as to be invisible. It is intensely pungent, dilutions of one part in a million in water imparting perceptible warmth to the tongue and lips. It is soluble in the ordinary organic solvents and slightly in water, and is removed from aqueous mixtures by petroleum ether, hence in conducting analysis with the procedure of immiscible solvents, capsaicin is one of the first of the common substances encountered.

Capsaicin has the probable composition, $C_{18}H_{27}NO_3$, but it is not an alkaloid. It apparently contains a phenolic hydroxl and a methoxy group. Its alcoholic solution when treated with dilute ferric chloride, develops an evanescent greenish-blue color. An alcoholic solution acidulated with hydrochloric acid, and treated with a little platinic chloride develops an odor like vanilla when allowed to evaporate spontaneously. A solution of capsaicin in concentrated sulphuric acid develops a violet color on adding sugar. Nelson [1] has shown that it is a condensation

[1] J. Am. Chem. Soc., 1919, 41, 1115.

product of vanillyl amine (3-hydroxy-4-methoxybenzylamine) and a decylenic acid:



The color, and odor reactions above described are of no value for detecting capsaicin in the ordinary run of medicinal preparations and beverages because of the comparatively small amount that is present in the quantity of the sample which can be sacrificed for analytical work. The only satisfactory method of detection is one based on its physiological action, and this must be conducted in such a way as to exclude the possibility of confusion with piperin and ginger principles.

Lawall describes a method for detecting capsaicin which excludes the possibility of ginger bodies being present.

If the sample contains alcohol add sufficient sodium hydroxide to render it slightly alkaline and then evaporate until the alcohol is expelled. Transfer the residue to a separatory funnel with water, acidify with sulphuric acid and shake out with ether. Separate and evaporate the ether, add alcoholic potash to the residue, and heat for half an hour in a boiling water-bath under a reflux. Evaporate to dryness, take up the residue in water, and extract with ether. Separate ether extract and wash with water until the washings are neutral to litmus. Then allow ether to evaporate spontaneously in a dish. The tip of the tongue is then applied to the residue or to the center of the bottom of the dish where a residue would naturally concentrate when the presence of capsaicin will be apparent by its characteristic burning sensation. If but a minute amount is present it may take a few minutes for the reaction to develop, and in some cases it may be necessary to apply the entire residue to the tongue.

Piperin, the alkaloid of pepper which would appear in the same fraction as capsaicin, is readily distinguished by means of its characteristic color tests.

The comparative pungency of capsicum is determinable by physiological means. By True's method[1] a small weighed quantity of the powder is placed in a mortar with a small weighed quantity of cane sugar and triturated until the powders are completely mixed and reduced to great fineness. If on tasting a small portion of the powder, the sensation of pungency is noted, further weighed quantities of sugar are added until the pungency can no longer be perceived. A ratio is thus established between the original weight of the capsicum used and the weight of the sugar necessary to bring the sensation of pungency just to the point of disappearance.

[1] Bulletin U. S. Dept. Agri. No. 43, Bu. Plant Industry, Dec. 16, 1913.

Scoville [1] proposes an analogous procedure, using an alcoholic extract of the drug. One gram of the powdered sample is macerated overnight with 100 mils of alcohol and after thorough shaking is filtered. The alcoholic solution is then added to sweetened water in definite proportions until a distinct but weak pungency is perceptible on the tongue. Powdered capsicums may run from 1–20,000 to 1–100,000, and oleoresin may test 1–150,000 and upwards.

GINGER

Zinziber officinale (Scitamineæ) possesses a pungent rhizome employed in dyspepsia, flatulent colic, and enfeebled conditions of the alimentary canal. It is an agreeable addition to bitter infusions and tonic mixtures, and is used to a large extent in remedies for diarrhea, dysentery, cholera morbus, colic, nausea, etc.

Extract and tincture of ginger are popular household remedies. The oleoresin prepared similarly to the oleoresin of capsicum enters into the composition of pill and tablet formulas and is also used in the preparation of extracts for ginger ale. The powdered rhizome is combined with pancreatin, pepsin, and other digestives, and bismuth subcarbonate in popular remedies for impaired digestion which are sold in powder form.

The pill and tablet formulas containing ginger are of the following type: aloes, ferrous sulphate, and Conium; aloin, Cascara sagrada, belladonna, strychnin, and Podophyllum; Colocynth, jalap, gamboge, rhubarb, and calomel; cinchonidin, cardamom, gentian, pimento, pepsin, and hydrochloric acid; pepsin, pancreatin, and Nux Vomica; pepsin, pancreatin, bismuth subnitrate, Nux Vomica, and sodium bicarbonate; sodium salicylate, Capsicum, and cardamom; aloes, ferrous sulphate, black hellebore, myrrh, soap, and canella (female pills); pepsin, charcoal, and magnesia (dyspepsia lozenges).

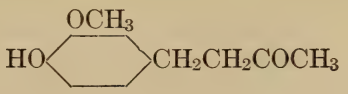
Aromatic tincture N.F. contains ginger, cinnamon, cloves, cardamom, and galangal root.

Ginger is obtained chiefly from India, the West Indies and certain parts of Africa. The Indian variety is known as black ginger and is prepared by scalding the cleansed root in boiling water and rapidly drying it. In Jamaica the best roots are deprived of their epidermis and dried carefully in the sun, this variety being known as white ginger. The Indian variety is sometimes found coated with calcium carbonate or sulphate, and again artificially bleached to simulate the white ginger from Jamaica.

Ginger contains from 2.5 to 7 per cent of resinous material and fixed oil. Its flavor and characteristic odor depends on a volatile oil, and its

[1] J. Am. Pharm. Ass., 1, 453.

pungency on the resinous constituents. The pungent principle has been isolated and is, like capsaicin, a derivative of vanillin, having the following composition:



It is called Zinzerone by its discoverer, Nomura.

Kraemer and Sindall [1] obtained the accompanying analytical data with authentic commercial samples of ginger from different sources:

	Total Ash	Ash insol. in 10 per cent HCl	Cold H_2O extract	Volatile Ether Extract	Non-vol. Ether Extract	Alcoholic Extract	Crude fiber	Starch	CaO
African . .	5.74	1.15	12.62	7.17	8.49	7.20	2.62	55.07	0.12
Calcutta .	7.47	2.02	14.20	3.06	6.50	6.40	5.46	47.89	0.13
Calicut . .	5.64	0.55	13.08	4.62	6.42	7.76	1.64	48.77	0.33
Cochin . . .	6.43	0.85	14.30	7.03	6.68	8.04	3.06	52.00	0.58
Jamaica . .	3.88	0.45	15.54	3.23	7.30	5.80	1.44	58.97	0.17
Japan . . .	6.16	0.69	14.40	7.39	7.01	10.48	1.60	55.97	1.68

Kebler and Kimberly [2] found that Calcutta and Japanese gingers are not suitable for the preparation of the U. S. P. tincture, and that a properly prepared tincture should contain not less than 90 per cent alcohol and from 1.25 to 1.75 per cent non-volatile matter.

The presence of ginger in medicinal preparations is usually noticed by the aromatic vapors evolved on evaporating an alcoholic extract of the sample, and by the characteristic pungency of an aqueous decoction of the evaporated residue left by the alcohol. The absence of capsaicin may be determined by the procedure given under capsicum.

In certain doubtful cases the actual identity of ginger may be desirable. Seeker has suggested a method for accomplishing this:

Dilute 10 mils of the extract to 30 mils, evaporate off 20 mils, decant into a separator and extract with an equal volume of ether. Evaporate the ether spontaneously in a porcelain dish and to the residue add 5 mils of 75 per cent sulphuric acid and about 5 mg. of vanillin. Allow to stand for fifteen minutes and add an equal volume of water; when in the presence of ginger extract an azure-blue color develops.

The actual value of this method is probably overestimated because it appears from recent work that certain hydrocarbon-like constituents of volatile oils will produce a similar if not an identical shade of color when subjected to the same procedure. Hence it would be advisable

[1] Am. J. Pharm., 80, 303.

[2] U. S. Dept. Agri. Bu. Chem. Bull., 152, 244.

to consider with great caution any positive evidence as to the presence of ginger when based on this test alone.

ASARUM CANADENSE. CANADA SNAKE-ROOT

Asarum canadense (Aristolochiaceæ), wild ginger, or Canada snake-root, possesses a pungent root stock. It is used medicinally as an aromatic, stimulant, carminative, and diaphoretic. It is prescribed with Cinchona for certain forms of low fever. It is also combined with ipecac in syrupy mixtures.

A. acuminatum and A. reflexum are eastern plants resembling the above species, and their roots might be mistaken for Canada snake-root by an inexperienced collector.

Power examined the rhizome and found a volatile oil, resin, fat, an amorphous yellow coloring matter, uncrystallizable sugar, and a small quantity of a feebly basic principle. The volatile oil contained pinene, an isomer of borneol, asarol, which is perhaps identical with linalool, asarin a neutral substance, coeruline, and acetic and valeric esters of linalool.

SERPENTARIA. VIRGINIA SNAKE-ROOT

The rhizomes of both Aristolochia serpentaria and A. reticulata (Aristolochiaceæ) are official in the U. S. Pharmacopœia as Serpentaria. As a drug it has stimulant, tonic, diaphoretic, and diuretic properties, and is often used in low fevers either by itself or combined with Cinchona alkaloids. It is also used in dyspepsia and as a gargle for sore throat. The extract has been at various times recommended as an emmenagogue and as a cure for snake bite.

Virginia serpentaria, also known as serpentary, is found in rich dry woodlands from Connecticut to Michigan and southward. Texas serpentaria (A. reticulata) occurs in the Southwestern States, growing along river banks from Arkansas to Louisiana.

The crude drug will often be found mixed with other root drugs, including Spigelia, senega, and abscess root (Polemonium reptens), the latter resembling serpentaria closely except that it is nearly white.

Many other species of the genus Aristolochia of this country and of foreign habitat are used as drugs.

The characteristic constituents of the rhizome appear to consist of a bitter principle and volatile oil containing pinene, and esters of borneol which give the drug its camphoraceous odor and flavor. An alkaloid has been reported from a species of Aristolochia from South America, but no basic substance has been isolated from the plant growing in the United States.

GLYCYRRHIZINIC ACID AND LICORICE ROOT

Licorice root from Glycyrrhiza glabra and G. glandulifera (Fabaceæ) possesses a sweet principle which is employed for the purpose of masking the taste of other drugs, and the extract will be found in a great variety of medicinal compounds. As a drug, licorice is useful as an emollient and demulcent in coughs, catarrh, irritations of the bronchial and urinary organs, and other similar affections of the mucous surface.

It will be found in fluid extract aloes compound; with aloes and myrrh; in black cohosh compound; rhubarb compound, various sarsaparilla compounds; in compound quinin elixirs, with glyceroles of eriodictyon, heroin, etc., elixirs of Cascara sagrada and Berberis aquifolium; Taraxacum and wild cherry; eucalyptus, gentian; and many other bitter tonic compounds and bitter cough remedies. Aromatic elixir of glycyrrhiza and syrup of glycyrrhiza are national formulary preparations.

Compound licorice powder consists of powdered licorice root, senna, washed sulphur, sugar, and oil of fennel. Tully's powder consists of powdered licorice root, morphin sulphate, camphor, and calcium carbonate. Brown mixture consists of extract of licorice, powdered opium benzoic acid, tartar emetic, camphor, and oil of anise.

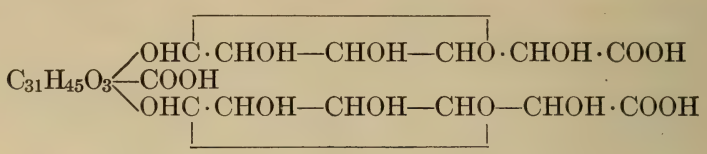
Among the tablet and lozenge formulas in which extract of Glycyrrhiza functionates as a demulcent or emollient may be mentioned ammonium chloride and cubeb with and without codein; Conium and cubeb; benzoic acid, cubeb, and belladonna; ammonium chloride, tolu, cubeb, senega, ipecac, and Hyoscyamus; ammonium chloride, cubeb, and cocain; Krameria, bismuth subnitrate, and opium; cubeb, tolu, and Sassafras; coltsfoot, cubeb, peppermint, tolu, Capsicum, and oil of anise; pine tar, eriodictyon, senega, and wild cherry; and coltsfoot, acacia, horehound, wild cherry, tolu, anise, cubeb, and Capsicum.

The commercial extract of glycyrrhiza or licorice paste is prepared by water extraction. It is a hard black mass, brittle, breaking with a shining fracture and almost entirely soluble in boiling water. Gums and resinous constituents are usually present and some varieties contain commercial glucose or corn syrup. This form is used almost entirely in the manufacture of chewing tobacco.

The fluid and solid extracts of the Pharmacopœia are prepared with ammonia and alcohol. Ammoniated glycyrrhizin is a scaly preparation of the sweet principle in the form of its ammonium salt.

The important constituent of the root and extract is glycyrrhizic acid or glycyrrhizin. It occurs in the root in soluble form, and by treating the extract with a mineral acid the compound is broken up and the crude acid is precipitated as a brown resinous mass, difficultly soluble in water and especially when acidulated. When pure it forms colorless

crystals, melting 195°. Chemically it is a diglucuronic ether of glycyrrhetic acid and by Tschirch is accorded the structural formula:



Housemann [1] reports that glycyrrhizinic acid contains nitrogen. In his investigation he evaporated a solution of the acid to dryness *in vacuo*, crystallized the residue twice from hot glacial acetic acid, and finally dried over potassium hydroxide *in vacuo*. Analysis of the product showed 58.37 per cent carbon, 7.72 per cent hydrogen, 1.09 per cent nitrogen. Three recrystallizations from glacial acetic acid raised the nitrogen to 1.89 per cent. The substance turned brown at 185° and partly melted with frothing at 203–205°. It was readily soluble in hot water, the solution gelatinizing on cooling.

Housemann found 2 per cent of sucrose in the root. The inner bark of both green and dried root, but not the outer bark or central part of the root, contain hemolytically active saponins, in addition to the saponigenin glycyrrhetic acid. These are extracted by 75 per cent alcohol but not by water or by alcohol weaker than 50 per cent.

Properly purified glycyrrhizin at a dilution of 1–20,000 has a lasting pure sweet taste.

In the analysis of medicinal products, glycyrrhizinic acid will appear when an evaporated alcoholic extract of the sample has been treated with water, filtered from any resinous constituents, and then treated with dilute sulphuric acid previous to shaking out with immiscible solvents. The appearance of a brown, resinous precipitate at this point is strongly indicative of glycyrrhizinic acid. It usually sticks to the side of the container and the liquid is readily decanted, the substance washed with ice water, or very dilute acid and then dissolved in ammonia and the filtered solution evaporated. The residue, which will have a scaly appearance, is soluble in water and the solution has a characteristic sweet taste.

Housemann [2] recommends the following procedure for the analysis of licorice paste:

Moisture and ash are determined in the usual manner.

Matters Insoluble in Cold Water.—Two grams of the extract are spread on the sides of a small, copper gauze basket, which is placed in a 100-mil cylindrical glass tube drawn out to a conical end and containing about 75 mils of distilled water. The tube is closed with a rubber stopper and agitated in a shaking machine until the paste is completely

[1] Amer. J. Pharm., 1916, 88, 97. [2] Amer. J. Pharm., 84, 1912, 531.

disintegrated (one-half hour to one hour) and then whirled in a Babcock centrifuge for fifteen minutes at 1000 revolutions per minute. The clear liquor is poured off and the sediment stirred up with fresh water and whirled for a further fifteen minutes. After pouring off the liquor, the sediment is washed into a tared glass dish, evaporated and weighed.

Most licorice pastes, when freshly made, will contain not more than 3 per cent by weight of matters insoluble in cold water, unless made from very starchy root or from liquor which, having been partly chilled, contains gelatinized starch. A paste containing more than this amount should be dissolved without the aid of a shaking machine by suspending in cold water, as the use of the shaking machine is found to give low results with pastes containing much insoluble matter. Many experiments have shown that fifteen minutes is a sufficient time to centrifuge at 1000 revolutions, the results being identical with those obtained by twenty-four hours settling in a tall jar.

Matters Insoluble in Hot Water.—This estimation is carried out in a similar manner to the preceding determination, using hot water.

Starch and Gums.—Two grams of licorice mass are dissolved in 10 mils hot water, in a centrifuge tube similar to that used for "matters insoluble in cold water." The solution is cooled and 20 mils 80 per cent alcohol (by volume) are added with stirring. Fifty mils 95 per cent alcohol are then added gradually with stirring. After allowing to stand two hours, which time is found sufficient to precipitate all starch and gummy matters, the contents of the tube are centrifuged. After pouring off the clear liquor, the precipitate is stirred up with 80 per cent alcohol and centrifuged. This operation is carried out three times in all. The precipitate, consisting of starch and gums, and the mechanical impurity in the paste, is washed into a tared dish, evaporated, and weighed. The mechanical impurities (matters insoluble in hot water) are deducted, to give the true weight of starch and gums.

Glycyrrhizin.—The clear 80 per cent alcoholic liquor, poured off from the starch and gums, is evaporated just to dryness *in vacuo* on a water-bath. The residue is transferred to a small conical beaker with 30 mils water and after cooling to 15° C., the crude glycyrrhizin is precipitated with 3 mils dilute sulphuric acid (10 mils conc. sulphuric acid to 300 mils water). After standing for two hours (twelve to twenty-four hours, as usually recommended, is unnecessary and gives lower results) at a temperature of about 10° C., the contents of the beaker are cooled in ice for half an hour, and the clear supernatant liquor poured through a small filter. The glycyrrhizin is washed four times by decantation with ice water, in which it is practically insoluble. The glycyrrhizin in the beaker, together with any that may have beeen transferred to the paper, is dissolved in dilute alcohol. Two drops of 5 per cent ammonia are added

to neutralize traces of sulphuric acid, and the solution is transferred to a tared dish, evaporated, and the crude glycyrrhizin weighed.

Sugars.—The filtrate and washings from the glycyrrhizin, amounting to about 70 mils, are received in a 100-mil graduated flask. Enough of a concentrated solution of basic lead acetate is added to precipitate both the sulphuric acid and the resins, bitter substances, coloring matters, etc. (3 mils are usually sufficient). The liquid is made up to 100 mils and an aliquot filtered into a 100-mil graduated cylinder. The excess of lead is exactly removed with sodium carbonate, the liquid made up to 100 mils again, filtered, and titrated with Fehling's solution before and after inversion.

The method for the determination of glycyrrhizin can be used to advantage in estimating that substance in commercial ammonium glycyrrhizinate.

COMPOUND LICORICE POWDER

The moisture and ash can be estimated by the ordinary methods. Glycyrrhizin, sugar, and water-soluble extract are determined by digesting 5 grams of the sample with 250 mils of water for twenty-four hours with occasional agitation. After settling, aliquots of 50 mils each are used for the water soluble extract and sugar determinations, and 100 mils for the glycyrrhizin. The technique to be employed in estimating glycyrrhizin is the same as in licorice paste.

The total sulphur is determined by oxidizing 1 gram of the powder with fuming nitric acid and a little potassium nitrate or chlorate, and finally precipitating with barium chloride.

The anthraquinone derivatives of the senna can be estimated by the method described on page 62.

Parkes and Major [1] who outlined a procedure essentially like this one examined 13 samples of compound licorice powder and obtained the following data: moisture 3–7.9 per cent; ash 4.6–6.2 per cent; water extract 61.1–63.9 per cent; sucrose 48.3–50.3 per cent; glycyrrhizin 1.2–2.9 per cent; total sulphur 7.8–9.2 per cent.

Tschirch and Gauchmann report the presence of glycyrrhizinic acid in the root of Periandra dulcis and the bark of Pradosia lactescens, both from Brazil.

Eupatorium rebaudianum contains two sweet principles of the nature of glucosides. They have been separated by dissolving in methyl alcohol and pouring into absolute alcohol, which precipitates rebaudin and leaves eupatorin in solution. The former is soluble in water, methyl alcohol, and dilute acids, but insoluble in ethyl alcohol and ether. The latter is soluble in water, methyl and ethyl alcohols, and acids, but insoluble in ether. They are therefore essentially different from glycyrrhizinic acid.

[1] Analyst, 1914, 39, 160.

This eupatorin must not be confused with the substance of the same name which has been extracted from Eupatorium perfoliatum or common boneset.

CANTHARIDES AND CANTHARIDIN

Cantharidin occurs in the anatomy of a number of insects. The species Cantharis versicatoria is official in our Pharmacopœia. If kept perfectly dry the activity is retained for a long time, but it is subject to the attack of a small worm which consumes the interior parts, and the vesicating power is lessened to a considerable degree by the attack of this pest.

Some of the other species of insects containing cantharidin include Mylabris oculata, Thunb; M. holocericia, Kley; Decatonia lunata, Pallas; Electica wahlborgia, Fabr; Cantharis vellata; Lytta cœlestina; Cantharis vittata; C. cimeria; C. marginata; C. atrata; C. vulnerata and others.

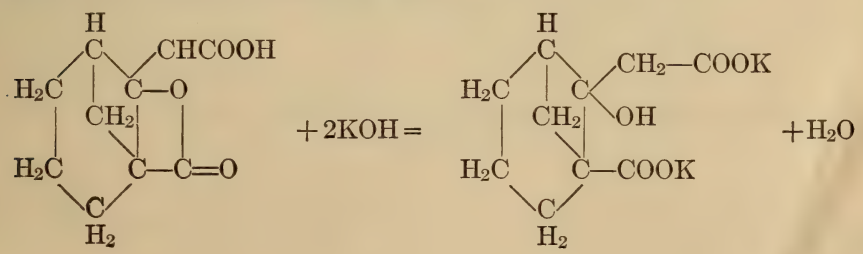
Cantharides as a drug is used principally in remedies for the stimulation of the urinary and genital organs, in hair tonics, and locally for blistering purposes. It is reported to be of value in producing sexual excitement.

It is often combined with phosphorus, Nux Vomica, damiana, and zinc phosphide; with belladonna, saw palmetto, and corn-silk; and with guaiac, aloes, and ferrous sulphate. Cantharidal collodion is a pharmacopœial preparation of this drug which furnishes a ready medium for the exhibition of its vesicating properties.

Cantharidin occurs partly free and partly combined and the nature of the combination is unknown. It is volatile on evaporation with solvents, but can be dried at 60° for two hours without loss. It is fairly soluble in acetone, chloroform, and ethyl acetate, moderately in alcohol, ether, and hot water, but only very slightly in cold water and petroleum ether.

Cantharidin forms colorless, shining, neutral, rhombic leaflets, melting 218°, and subliming at higher temperatures in white needles.

It is a monobasic acid and a β-lactone. Potassium or sodium hydroxide break the labile β-lactone ring, and by this means cantharidin forms the alkali salt of dibasic cantharidic acid.



These alkaline salts are crystalline and on treatment with a mineral acid cantharidinic acid is set free, which soon loses a molecule of water and passes into cantharidin. The alkali cantharidinates are used medicinally as remedies for phthisis.

In the general scheme of qualitative analysis of medicinal preparations cantharidin will, in part, be found in the aqueous solutions of the evaporated alcoholic extract of the mixture from which it will be separated in the ether fraction. As it gives no characteristic color resctions and as it is in such small quantity usually that a melting-point determination is impossible, it is necessary to resort to a physiological reaction which depends on its vesicatory power. For this purpose the residue is dissolved in chloroform and the solution applied drop by drop to the under side of the forearm above the wrist. As each drop evaporates another is applied in the same spot. If any cantharidin is present the tingling effect will soon be apparent and the blister will appear.

Assay of Cantharides.—Twenty grams of cantharides, in fine powder, are moistened with 3 mils of strong hydrochloric acid, and extracted, in a Soxhlet apparatus, with 80 mils of benzene for two hours. The residue is washed with 25 mils of benzene, and the benzene removed from the extract by distillation and, finally, by a current of air. The distilled benzene is shaken with successive portions of 20 mils, 20 mils, and 10 mils of a 1 per cent solution of potassium hydroxide to recover any traces of cantharidin which have distilled over, and the mixed alkaline solution is acidulated with hydrochloric acid, made up to 105 mils with distilled water, and added to the residue of fat and cantharidin left after distilling off the benzene. The mixture is boiled for ten minutes under a reflux condenser, and so soon as the layer of fat has separated, 100 mils of the hot aqueous layer are pipetted off. The boiling is then repeated four times for five minutes after addition each time of 50 mils of distilled water, 50 mils of the separated aqueous layer being removed after each boiling. The mixed aqueous solution is acidified with 3 mils of strong hydrochloric acid, and shaken with successive portions of 30, 30, 20, and 20 mils of chloroform. The chloroform extract is distilled in a tared flask, the residue washed with quantities of 5, 5, and 2 mils of a mixture of equal parts of absolute alcohol and petroleum spirits saturated with cantharidin, and the cantharidin dried at 60–65° C. until of constant weight.

DETERMINATION OF CANTHARIDIN IN TINCTURE, OIL AND PLASTER OF CANTHARIDES

Tincture.—Fifty grams of the tincture, 25 grams of water, and 1 mil of sodium carbonate solution (1 : 2) are evaporated together to dryness

on the water-bath. The residue is taken up with 10 mils of water, treated with 2 mils of hydrochloric acid (1 : 4), and shaken out with 10 mils of chloroform, which has been used previously to rinse out the flask. After separation, the chloroform is drawn off, and the acid aqueous liquid is again shaken out with 5, 5, and 5 mils of chloroform in succession. The chloroform extract is evaporated at a gentle heat, the last traces of solvent being blown off with an air current. After standing for twelve hours, the air-dried residue is treated once with 10 mils, then four times successively with 5 mils of light petroleum spirits. These petroleum spirit washings are passed through a small filter. The air-dried residue and this filter are then washed, first with 10 mils of water containing a drop of ammonium carbonate solution, then with pure water, and dried at 50° C. The dry residue is dissolved in a little acetone, and passed through the dry filter, into a small tared flask. The solvent is evaporated off at a gentle heat by the aid of a current of air, and the brownish-yellow residue is dried, first at 50° C. and finally in the water oven, till of a constant weight.

CHAPTER XIII

BOTANICAL DRUGS

WHITE PINE

THE inner bark of the white pine, Pinus strobus (Pinaceæ), is used as an expectorant and is one of the ingredients of white-pine syrup. The extract of the drug is usually combined with several of the following: wild cherry, balsam poplar buds, spikenard, Sanguinaria, sassafras, squill, senega, ipecac, opium, camphor, morphin, chloroform, methyl salicylate, potassium nitrate, glycerin, codein, Cannabis sativa, Eriodictyon, ammonium chloride, tar, tolu, and honey.

Compound syrup of white-pine contains white-pine, wild cherry bark, balsam poplar buds, spikenard, Sanguinaria, sassafras, morphin, and chloroform.

Coniferin, $C_{16}H_{22}O_8 + 2H_2O$

Coniferin occurs in the cambium sap of coniferous trees. It forms white satiny needles with two molecules of water of crystallization, effloresc-ing in dry air and becoming anhydrous at 100°, melting at 185°. It is soluble in alcohol and slightly in hot water, insoluble in cold water and ether. The aqueous solution has a bitter taste and is lævorotatory $(\alpha)_D^{20} = -66.9°$. It dissolves in concentrated sulphuric acid with a red color, a deep blue resinous substance separating on dilution with water. When moistened with carbolic acid and treated with concentrated sulphuric or hydrochloric acid, it rapidly acquires a deep-blue color. It gives no reaction with metals nor Fehling's solution.

Coniferin is oxidized to vanillin when warmed with chromic acid. Emulsin hydrolyzes it to coniferyl alcohol and dextrose, but when dilute acids are employed the coniferyl alcohol polymerizes or resinifies.

Coniferyl Alcohol. $C_6H_3-OCH_3 \cdot OH \cdot C_3H_4OH \cdot 3.2.1$

Coniferyl alcohol melts 73–74°, soluble in alcohol, ether, and alkalies, with difficulty in water. It is reduced by sodium amalgam to eugenol, and oxidized by chromic acid to vanillin.

TRITICUM. COUCH-GRASS. DOGGRASS

The rhizome of Agropyron repens (Graminæ) furnishes the commercial triticum. It is chiefly employed in kidney troubles, and its presence may be suspected in any mixture recommended for cystitis and irritable conditions of the bladder. It is usually combined with one or more of the following: buchu, Hydrangea, corn silk, pichi, Viburnum prunifolum, atropin, borates, potassium bicarbonate, and benzoic acid.

No examination has been made of the constituents of this drug. If it is suspected in a mixture, the sample should be diluted with water, centrifuged and any vegetable residue at the bottom of the tube carefully examined under the microscope for the presence of characteristic tissue.

SAW PALMETTO

The ripe drupe of Sabal serrulata syn., Serenoa serrulata (Palmæ), a small palm growing in sandy soil in the Southeastern States, furnishes the drug.

Saw palmetto is considered valuable in a variety of conditions and may be found in tonics, remedies for diseases of the mucous membrane of the nose and throat, and for abnormal and irritated conditions of the urinary tract, and the organs of generation. It is combined with cantharides, belladonna, and corn silk; with Nux Vomica; with coca, kola, and Apium graveolens; with santalwood oil, and with olive oil.

The fresh fruit contains a volatile oil, and there is present in the drug a green or brownish fixed oil, consisting of the esters of a number of fatty acids including caproic, caprylic, capric, lauric, palmitic, and oleic. Resins and glucose are present.

Mann,[1] who has done some phytochemical work with this drug, concludes that the so-ca led volatile oil which is contained in the alcoholic extract is not a volatile oil in the generally accepted sense of the term, but a mixture of ethyl esters of fatty acids, formed by condensation of the free fatty acids, which are naturally contained in the berries, with alcohol.

IRIS VERSICOLOR AND IRIS FLORENTINA

There are some twenty-one species of Iris growing in North America, but only one of these, Iris versicolor (Iridaceæ), the larger blue-flag, has been used as a drug. The root is the portion employed, and while the therapeutic value of the freshly gathered material appears well established, the activity is apparently lost on standing, and much of the material that is sold on the market is probably inert.

[1] Amer. J. Pharm., 1916, 88, 517.

The extract of the rhizome and roots and a more or less purified form of the resinous constituents in the character of a concentration termed Irisin or Iridin, are the ordinary forms in which Iris is administered. In liquid preparations Iris occurs with Stillingia, Bicuculla canadensis, Chimaphila, Sambucus canadensis, Xanthoxylum berries, and coriander (Stillingia compound; with Stillingia, Bicuculla, Xanthoxylum bark, and potassium iodide; these preparations being designed for alterative and chologogue purposes. Iris is credited with great efficiency in liver complaints and hence is often combined with Podophyllum resin. In pills and tablets it occurs with Podophyllum, Nux Vomica, Capsicum, and Veronica virginica; with Podophyllum and strychnin; with Podophyllum, Hyoscyamus, and strychnin; with Podophyllum, Sanguinaria, and Euonymus; with Xanthoxylum, Stillingia, Arctium lappa, Phytolacca, and red clover blossoms.

Power and Salway [1] examined a commercial sample of Iris versicolor, finding it free of basic or glucosidal constituents, and in an aqueous decoction of the alcoholic extract, identified isophthalic acid, salicylic acid, tannin, and sugar yielding a *d*-phenylglucosone, melting 212°. The portion of the alcoholic extract insoluble in water consisted principally of a soft dark resin which amounted to about 8.7 per cent of the weight of the drug. From it were separated a phytosterol, $C_{27}H_{46}O+H_2O$, melting when anhydrous, 148° $(\alpha)_D = -35.6°$, in chloroform, myricyl alcohol, heptacosane, $C_{27}H_{56}$, ipuranol and a mixture of lauric, palmitic, stearic, cerotic, oleic, and linolic acids.

IRIS FLORENTINA

The root of I. florentina, the white flag or orris, was formerly employed as a cathartic and emetic, but at present finds its chief use in dentifrices, bath, toilet, and hair powders. It has a limited use in surgical work because of its great absorptive power.

Orris root contains a large percentage of starch and 0.1–0.2 per cent of volatile oil, which consists chiefly of myristic acid, with a ketone to which the name irone (ionone?) has been given, and to which the odor of the root is due. The odor of the pure ketone is pungent, and in the concentrated form seems to differ entirely from that of the violet, but the violet aroma becomes apparent when irone is dissolved in a large amount of alcohol and the solution evaporated.

CROCUS SATIVUS. SAFFRON

Crocus sativus (Iridaceæ) furnishes a drug closely allied to those just mentioned. It was formerly used as an antispasmodic and narcotic

[1] Amer. J. Pharm., 1911, 83, 1.

emmenagogue, but is now mainly a coloring and flavoring agent. It is still a component of pills containing aloes, myrrh, rue, and savine; of Warburg's Tincture; and of some Cinchona preparations.

Its high price has made it an attractive subject for adulteration, and though its importance as a drug is slight, much attention has been devoted to suppressing the traffic in the adulterated product.

The plant is perennial, rising from a corm, the flowers being lilac-purple with orange-red stigmas, which furnish the article known commercially as saffron. It should not contain the yellow styles. Dried saffron has about 7.5 per cent ash. When chewed it imparts an orange-red color to the saliva.

It contains a volatile oil. To water it yields, among others, a yellow substance to which the name crocin has been given. The yellow substance is also soluble in dilute alcohol, but only slightly in absolute alcohol.

The adulterants include the florets of species of compositæ, Calendula, Carthamus, and Arnica, fixed oils, glycerin, mineral matter, exhausted saffron dyed with coal-tar colors, and factitious products of which "Feminella" is a type, and consisting of florets of Calendula or other flowers colored to imitate the characteristic shade of saffron.

Vicari [1] recommends the use of sulphomolybdate reagent (60 mils conc. sulphuric acid and 40 mils 10 per cent sodium phosphomolybdate) for detecting Carthamus in saffron. The powder is spread over a glass slide in a thin coating without lumps. A drop of the reagent is allowed to fall upon the powder and well mixed with it. A greenish-blue color soon develops and then a cover glass is gently pressed down on the slide. Under a microscope of 50 diam. magnification, the particles of Carthamus are detected by their reddish color in the midst of the blue particles of saffron. If the particles of saffron are somewhat voluminous, or if the preparation of the powder for the microscope is not properly done, the coloration may be masked. An indication of the presence of Carthamus is furnished by observation under the microscope (100 diameters magnification) of the pollen grains. These are composed of two membranes, the outer being hard, resistant, and granulated exteriorly, the inner soft and delicate, and filled with a relatively dense, hyaline, protoplasmic liquid. The outer membrane is pierced with three symmetrically arranged openings, through which the inner issues, forming three typical protuberances. Under the microscope and in the presence of the reagent the outer membrane becomes colored brown, while the protuberances gradually elongate, turn a bright greenish blue, and finally take on sac-like formations, on account of the endosmosis of the reagent through the membrane increasing the tension of the internal protoplasmic substance. In time the reagent attacks the outer membrane, exposing to view its structure,

[1] Mitt. Lebens. Hyg., 1915, 6, 195.

thickness, and granulation. Sometimes the complete inner membrane will break intact through the weakened outer. The pollen grains of saffron under the action of the reagent merely turn blue, without modification or swelling.

MATICO

The constituents of matico reported by recent investigations as occurring in the drug differ considerably from those which were reported when it first came into use as a medicine. This may be due to the fact that different species figure in the investigations, or that changed conditions of climate, environment, or source have altered the characteristic components.

The official drug is supposed to be the leaf of Piper angustifolium (Piperaceæ), and according to Thoms it is hard to find this leaf in a pure, unadulterated condition. Some consignments often consist of P. lineatum either in whole or in part, and these are sometimes admixed with unidentified leaves.

Dr. Rusby states that the plant producing matico is a native of the Andes of Peru and Bolivia; the so-called matico plants of Mexico, Brazil, and other sections are different species. At one time all of the shipments of matico offered for import were of P. mandonii, and had a much weaker odor and taste than the genuine.

In tropical America the term "matico" is applied to a number of astringent and hemostatic leaves, several of which are from species of Piper, and of importance in commerce. These include P. aduncum, P. camphoriferum, P. angustifolium var ossanum, P. acutifolium subverbascifolium, P. mollicomum, and P. asperifolium.

In looking up the history of this drug an interesting story is found to be connected with it, though it must be taken with reserve, as it has been applied to other vulneraries of tropical America. According to the legend the name "Matico" was first applied by the inhabitants of Quito to Eupatorium glutinosum, the properties of which were discovered by a soldier called Mateo, better known under the name of Matico (little Matthew), who, wounded in action, applied the leaves with good effect in stopping bleeding. Another plant, Waltheria glomerata, possessing similar properties, has obtained the name Matico in the Panama region, where it is also known as Pado-del-soldado (Soldier's tree), and a story similar to that given above is connected with it.

It is interesting to note that E. glutinosum sometimes occurs in shipments of matico and is now considered an adulterant.

Matico occurs in remedies for diseases of the genito-urinary organs, and is usually administered in the form of an oleoresin, combined with copaiba, cubeb, and santalwood oil. It is also used to treat bronchial

affections, chronic diarrhea, and hemorrhage of the lungs, kidneys, and gastro-intestinal tract. Its extract is found in elixirs with Hydrangea and Uva Ursi.

Maticos at one time yielded an oil which contained a product to which the name "Matico camphor" was given. This product does not appear in the distillates from any of the maticos at present on the market. Schimmel finds that there are marked differences in the products of distillation from different lots of matico, even though there may be little difference in the odor and appearance of the drug. Schimmel never finds matico camphor, but does get asarone and often methyl eugenol.

Thoms reports the following characteristics of oils from different species of Piper which have been found in matico shipments:

Oil from P. angustifolium of undoubted origin contained parsley apiol, dill apiol, a hydrocarbon boiling 121–130° under 13 mm., and a small amount of a phenol ether. Neither matico camphor nor asarone were found. Dill apiol is 1-allyl-5-6-dimethoxy-3-4-methylene dioxy-benzene.

Oil from P. camphoriferum (DeCandolle) has specific gravity .9500, $(\alpha)_D = +19° 21'$ and contained camphor, borneol, terpenes and sesquiterpenes.

Oil from P. lineatum had specific gravity .958, rotation $+8° 45'$, and contained a large quantity of sesquiterpene but no camphor.

Oil from a variety styled P. angustifolium var. ossanum yielded a camphor mixture.

The properties reported for matico camphor by Kugler in 1885 showed it to have a melting-point of 94° C. and devoid of odor and taste. The impure substance possessed the characteristic odor of the drug and melted 89–103°. Matico camphor floats on water with a rotatory motion. It is soluble in alcohol, ether, chloroform, and benzol, and is not attacked by alkalies. With sulphuric acid it gives a yellow color, changing to red and violet; with a mixture of sulphuric and nitric acids it gives a yellow changing to violet and blue. Hydrochloric acid produces a violet color, changing to blue and green, the compound yielding brown crystals with ether, which have an ethereal odor and show a green fluorescence.

Besides the volatile oil the matico leaf contains tannin, resinous constituents, and an acid which has been called artanthic acid.

CUBEB

The fruit of the cubeb contains substances of reputed value for the relief of diseased mucous membranes, and preparations containing the extract or the oleoresin are widely used for gonorrhea, gleet, and catarrhal inflammation of the urinary and other mucous tracts. The drug consists of the full-grown unripe fruits of Piper cubeba (Piperaceæ).

The oleoresin, which is an evaporated ethereal extract of the drug, is combined with copaiba alone and with other substances such as santalwood oil, turpentine, oleoresin matico, extract of buchu, extract of Krameria, iron chloride, salol, and pepsin; salol, pepsin, santalwood oil, and olive oil. Oil of cubeb is sometimes substituted for the oleoresin, and in pills and tablets we find copaiba and cubeb combined with guaiac and ferric citrate; turpentine and ferrous sulphate; santalwood oil, etc. Cubeb, either in the oleoresin, extract or powdered form, is also combined in pills and tablets with ferrous sulphate and Krameria; with licorice and ammonium chloride, sometimes with codein; with licorice and Conium maculatum; with licorice, ammonium chloride, tolu, ipecac, senega, and Hyoscyamus; with licorice, ammonium chloride, and cocain; with rhubarb, angelica, Inula, saffron, fennel, gentian, zedoary root, myrrh, white agaric, camphor, and aloes in Warburg's Tincture. It occurs in several lozenge formulas with licorice and sassafras oil; with colts foot, licorice, sugar, acacia, horehound, wild cherry, anise, tolu, and Capsicum; with licorice, tolu, and sassafras; with colts foot, peppermint oil, licorice, tolu, anise, and Capsicum, and in other combinations of the same substances. It occurs in liquid products combined with buchu, nitrous ether, juniper berries, and Uva Ursi; with senna, Collinsonia, Hydrastis, Bikukulla, copaiba, and potassium iodide, and it is used as one of the ingredients of inhalant combinations with such substances as tolu, iodin, camphor, carbolic acid, and glycerin.

A number of other species of Piper yield fruits resembling cubeb such as P. clusii of West Africa; P. borbonense of Bourbon; P. sumatranum and P. pedicellosum of India. The fruits of Toddalia lanceolata (Rutaceæ), of Litsea citrata and L. cubea (Lauraceæ) have been sold and substituted for genuine cubeb.

The constituents of genuine cubeb thus far definitely determined are a volatile oil amounting to 10–20 per cent and consisting chiefly of terpenes, sesquiterpenes and sesquiterpene hydrate called cubeb camphor; resinous matter; a bitter principle, cubebin; an acid called cubebic acid (supposed to be the cause of the characteristic red color produced when an ethereal extract of cubeb is treated with sulphuric acid); starch, and fixed oil.

The stem-free fruit yields about 20–25 per cent of its weight to ether. If a small portion of the ether-free extract is treated with a drop of concentrated sulphuric acid, 1 mil of ether added and rotated until the ether is evaporated, a crimson color is obtained. Adulterated samples give a red color with brown streaks intervening, while spurious products give a brown color and a mace odor.

Cubebin

Cubebin has the composition $C_{20}H_{20}O_6$. It forms white crystals melting 132°, $(\alpha)_D = -45.45$ in chloroform, soluble in alcohol and ether. It contains two hydroxyl groups. When dissolved in glacial acetic acid and dehydrated with hydriodic acid cubebinic ether results. This substance melts 78°, $(\alpha)_D = +23.04°$ in chloroform, forms white silky needles, soluble in alcohol, benzol, acetic acid, and chloroform, and but slightly in water. It contains no hydroxyl nor carbinol groups and is not acted upon by bromin, permanganate, or hydrogen peroxide. Cubebinic ether yields a primary alcohol, cubebinol, when reduced with alcohol and sodium. Cubebinol crystallizes in silky needles, melting 92°, $(\alpha)_D = +34.81°$ in chloroform, yielding an acetyl derivative melting 71°, $(\alpha)_D = +23.12°$ in chloroform and a benzoyl derivative melting 154–155°, $(\alpha)_D = -21.68°$ in chloroform.

Cubeb Oil

Cubeb oil is a viscid, light-green or bluish-green oil; colorless only when the last portions of the distillate which are blue, are not added; specific gravity .905–.925, $(\alpha)_D = -20$ to $-40°$. The solubility in 90 per cent alcohol varies, some oils being soluble in an equal part of the alcohol, others requiring a greater quantity. Oils distilled from old fruit are heavier than the normal and can be recognized by their action on potassium or sodium. A piece of freshly cut metal immersed in such an oil loses its luster, whereas an oil distilled from the fresh berries does not attack metal. The oil has the characteristic cubeb odor and a warm camphor-like taste, which finally becomes grating.

CANNABIS SATIVA. (CANNABIS INDICA)

The drug consists of the flowering tops of the pistillate plants of Cannabis sativa (Cannabinaceæ), an annual herb indigenous to Central and Western Asia and cultivated in India, Greece, and other tropical and temperate countries.

Cannabis is used in remedies for delirium tremens, certain forms of insanity, mania, excessive and painful cough, tuberculosis, migrain, itching of eczema, neuralgia, and severe pain of different kinds, and corns. It is also extensively employed in veterinary practice.

In pills or tablets it is combined with ergot; phosphorus and iron carbonate; with sumbul, Hyoscyamus and Valeriana; with arsenous acid and reduced iron; with Digitalis and reduced iron; with zinc phosphide and hyoscyamin; with phosphorus, strychnin, and damiana; with Hyoscyamus, Ignatia, opium, belladonna, Conium, Stramonium, and aconite;

with coca, Valeriana, strychnin, codein, arsenous acid, and ferrous carbonate; with strychnin, aconitin, zinc phosphide, and sodium arsenate; with morphin, Capsicum, Hyoscyamus, nitroglycerin, and oil peppermint; with quinin, Hyoscyamus, strychnin, acetanilid, and arsenous acid; with Hyoscyamus and the bromides of sodium, potassium, and ammonium.

Liquid preparations will follow the general type of the above mentioned combinations. The well-known " chlorodyne " type of remedies, popular for colic, cholera morbus, neuralgia, etc., contain Cannabis sativa, morphin, Capsicum, hydrogen cyanide, chloroform, and oil of peppermint. Anodyne mixtures contain Cannabis sativa, Hyoscyamus, chloral, and potassium bromide.

Corn remedies consist of a mixture of this drug and salicylic acid with collodion or an ointment base.

Cannabis contains from 15–20 per cent of a resin (called cannabin) consisting of a number of substances, one of which cannabinol, occurs as a red oily substance. Cannabinol appears to be the substance which gives the drug its peculiar active properties. It has the empirical formula $C_{21}H_{30}O_2$, and is very unstable. It has been separated from the drug and the method employed may be followed in isolating it for the purpose of testing. The sample is extracted with low-boiling petroleum ether and after recovering the solvent the resin is distilled under .1 mm. pressure in Claisen flasks fitted with Thorne's taps. The fractions passing over between 190–230° are united, dissolved in alcohol and subjected to a freezing temperature to remove paraffins. The alcoholic solution is distilled under diminished pressure in a current of hydrogen to remove the alcohol and the residue again fractionated, using the same procedure as above at a pressure of 0.1 mm. Cannabinol distills at 230° at this pressure. It is readily altered on exposure to air and light and loses its physiological activity. This change, due to oxidation, occurs in alcoholic and ethereal liquids, and is responsible for the loss of activity of the galenical preparations. It contains an hydroxyl. It forms a trinitroderivative and by the further action of nitric acid a complex substance, $C_{23}H_{29}N_3O_{12}$, and ultimately butyric and oxalic acids. Solutions of cannabinol in glacial acetic acid have a characteristic marked dichroism, being green by transmitted and red by reflected light. The addition of alkali hydroxides to an alcoholic solution produces a deep-red color which is discharged by the addition of an acid.

A petroleum ether extract of Cannabis or a petroleum ether extract of an evaporated alcoholic extract of the drug, on evaporation to dryness and treatment with absolute alcohol which has been saturated with dry hydrochloric acid gas, yields a bright cherry-red color which will disappear on dilution with alcohol or water. The same color is developed by concentrated sulphuric acid in acetone or acetic acid solutions of the extract.

Cannabis sativa or its active principle are best detected by their peculiar action on dogs. Shortly after receiving a suitable dose the animal vomits and becomes excitable, later incoordination follows, the dog loses control of its legs and the muscles supporting the head, so that when standing the feet are usually spread apart to maintain balance. A third stage finally develops in which the dog sinks to the floor as if exhausted, and passes into a deep sleep.

Preparations known to consist only of Cannabis may be administered directly by means of hard gelatin capsules, but where the drug is suspected in complex mixture the active principle should be extracted by means of petroleum ether, or if this is impracticable, with alcohol. The alcoholic extract may be administered directly, but if petroleum ether is used the solvent should be recovered and the residue tested.

Corn remedies are best treated with ether and the solution poured into absolute alcohol, when most of the inert material will separate out and the clear liquid can be used for testing. The mixture itself will often yield its Cannabis to the alcohol without dissolving in ether.

The animal's mouth is opened by forcing the thumb and index finger of the left hand between the jaws back of the teeth. The capsule is then placed on the back of the tongue with the right hand and the mouth quickly closed; while still holding the mouth shut, the animal can be made to swallow the capsule by slapping it on the throat.

The quantitative estimation of Cannabis sativa is at best only a measure of comparative activity. Any data obtained from any kind of a galenical preparation mean little except as to the relative activity of the particular product with respect to Cannabis. The activity of a dozen samples of drug answering the description of the Pharmacopœia may all come within an average and a dozen other samples of the same appearance fall far below them. A pill, a liquid mixture, or a solid extract may have a certain comparative potency measured in respect to a high grade sample of crude drug, but the figure obtained on the unknown cannot be used as a basis for stating the actual quantity of drug present.

The method of assaying Cannabis has already been described.

Within recent years the cultivation of the drug has been developed in the United States and the quality of the product is equal to any that was formerly imported. The plant is bisexual, the male and female flowers being produced on separate individuals, and the drug consists of the tops and unfertilized flowers of the female. The reason for this peculiar discrimination is somewhat obscure, for investigation has disclosed that the male tops which are culled out from the field, possess a physiological action of the same character with an equal degree of potency as the female portions.

In the eighth revision of the Pharmacopœia, one of the specifications

of the official drug was that its source should be the East Indies, though as an actual fact most of the shipments came originally from Greece. It is healthful to note that the East Indian myth has been left out of the ninth revision, but the unfertilized female tops are still the only portions recognized as representing the drug. There is undoubtedly good reason for demanding that the female tops should be unfertilized, but the reason for exclusion of the equally active male tops is not apparent.

There is still a lingering disposition in the trade to distinguish between so-called Cannabis Indica and Cannabis Americana, and an imported and often inferior article is quoted at a higher price than the native grown. Both products are one and the same, however, and there is no more reason for discriminating between them than there is for trying to draw a distinction between methyl salicylate and oil of gaultheria or between wild and cultivated ginseng or between first- and second-year Digitalis.

HOPS

Hops extract and the glandular powder called Lupulin are used medicinally for their tonic, sedative, and anaphrodisiac properties. They will be encountered in many tonic mixtures combined with malt, hypophosphites, glycerophosphates, Nux Vomica, etc.; and in various sedative formulas with Scutellaria, Cyprepedium, lactucarium, and bromides. They are also used in gonorrhea and other irritated conditions of the genitourinary organs. Their virtues seem to be adaptable either for the production or relief of sexual excitement, for combinations of hops with phosphorus, zinc, and strychnin are used as remedies for restoring sexual tone, and combinations with Scutellaria, bromides, and other sedative drugs are prescribed for producing the opposite effect.

The hop plant, Humulus lupulus, is now placed in the family Cannabinaceæ, and the male and female flowers are produced on separate plants. The male flowers are yellowish white and arranged in panicles, the female are pale green and disposed in solitary, peduncled aments. The part of the plant used is the fruit or strobile.

Lupulin is formed on the surface of the scale and in the dried fruit, existing in the state of very small granules. It is obtained by rubbing or threshing and sifting the strobiles, of which it constitutes from $\frac{1}{10}$ to $\frac{1}{6}$ by weight. It is a yellowish powder, with the characteristic hop flavor and under the microscope is seen to consist of globules filled with a yellow matter. It is inflammable and when moderately heated becomes somewhat adhesive. Lupulin should contain not more than 40 per cent of matter insoluble in ether and yield not more than 12 per cent of ash.

A vast amount of literature exists concerning the chemistry of hops, but much of it is vague and empirical and it has remained for Power,

Tutin, and Rogerson [1] to clear up many of the disputed points and to give us the first authoritative insight into the chemistry of the drug.

An alcoholic extract of hops on evaporation yields a volatile oil having a characteristic hop odor, extractive matter, and about 14–15 per cent of a dark-green oily resin. From the portion of the extract soluble in water there may be isolated small amounts of cholin and *l*-asparagin, tannin, potassium nitrate, a sugar yielding *d*-phenylglucosazone, melting 208°, and dark-colored, intensely bitter amorphous material. A volatile base with a coniin-like odor is also present, but has not been identified.

From the resin the following compounds have been isolated: ceryl alcohol; hentriacontane, $C_{31}H_{64}$; a phytosterol, $C_{27}H_{46}O$; a phytosterolin (phytosterol glucoside), $C_{33}H_{56}O_6$; a mixture of volatile fatty acids consisting of formic, acetic, butyric, valeric, a hexenoic acid, $C_6H_{10}O_2$, boiling 204–208° identified as β-isopropylacrylic acid, and nonic acid; saturated and unsaturated non-volatile acids including palmitic, stearic, cerotic, linolic, cluytinic, $C_{21}H_{42}O_2$, melting 69°; and an acid, $C_{20}H_{40}O_2$; an isomer of arachidic acid; and two new crystalline phenolic substances, humulol, $C_{17}H_{18}O_4$, melting 196°, with a pale-fawn color and a bitter taste, and xanthohumulol, $C_{13}H_{14}O_3$, melting 172°, orange-yellow in color and tasteless.

Humulol is soluble in sodium carbonate, but not in ammonium carbonate or hydroxide. The alkaline solution is yellow deepening on standing or when warmed. It gives a pale-yellow solution with concentrated sulphuric acid. Its alcoholic solution is uncolored by ferric chloride. It is insoluble in water, petroleum ether, or benzol, sparingly in ether and chloroform, more so in glacial acetic acid, and readily in alcohol and pyridin. When boiled with potassium hydroxide, humulol is resolved into *p*-hydroxybenzaldehyde, melting 118°, and giving a dark-violet color with ferric chloride, a crystalline acid, $C_{15}H_{14}O_5$, melting 210°, and complex viscous products.

Xanthohumulol is not decomposed on heating with potassium hydroxide, but dissolves with an intense yellow color. Its alcoholic solution is not colored by ferric chloride. With sulphuric acid the color is at first deep orange, but this soon fades to a colorless solution. It is readily soluble in ether, ethyl acetate, and pyridin, moderately in alcohol, and sparingly in benzol and glacial acetic acid.

The authors conclude that the bitterness of hops is not due to any single substance, such as the so-called "hop-bitter acid" or "lupulic acid," but it is attributed to a number of amorphous substances and humulol. Some of these bitter substances are soluble in water while others are in the resin. The differentiation of the resinous materials as α, β, and γ

[1] Trans. Chem. Soc., 103, 1913, 1267.

resins probably has little significance, and in our work at least does not call for further comment.

The presence of hop extract in a medicinal mixture is usually apparent by the odor. An aqueous decoction of an evaporated alcoholic extract of the sample will contain the amorphous bitter substance, which is removable by ether, after acidification, and thus easily separated from strychnin.

An ethereal solution of the resin, after first washing with ammonium carbonate, will yield humulol to sodium carbonate, and by subsequent shaking with potassium hydroxide the xanthohumulol is extracted. Both of these phenolic substances can be recovered by acidifying the alkaline solutions and shaking out with ether.

The identification of a small quantity of potassium nitrate in the sample will furnish further evidence of the presence of hop extract.

COCILLANA BARK

This drug, which has become a very valuable remedy for bronchial troubles, was discovered by Dr. Rusby. The tree, Guarea rusbii (Meliaceæ), is a native of Bolivia, and the thicker bark from the trunk and branches furnishes the drug.

The bark has a peculiar and rather nauseating odor and nauseous taste, and this characteristic is imparted to the extract. If ipecac is absent in remedies recommended for deep-seated coughs, the presence of cocillana may be suspected.

It contains a small quantity of an alkaloid, about 2.5 per cent of resinous matter, 2.5 per cent of fixed oil, and a white crystalline hydrocarbon-like body, melting at 80° C., sublimable, with a peculiar aromatic odor, soluble in ether, chloroform, acetic ether, and acetic acid.

PHYTOLACCA DECANDRA. POKEWEED.

The pokeweed is a familiar plant all over the eastern portion of the United States. It is a rapid grower, the stalks often attaining a height of nine feet with a spread of equal diameter. The dark-purple berries ripen in the autumn and both these and the root are gathered and used as drugs.

As an alterative the drug appears in remedies for syphilis combined with Stillingia, Smilax Pseudo-China (Bamboo brier), Xanthoxylum, and Lappa; or with red clover blossoms, Berberis aquifolium, Cascara amagra, Stillingia, Lappa, and potassium iodide, sometimes with Iris versicolor; as an antirheumatic it occurs with colchicin, digitalin, guaiac, and potassium iodide; and with lithium salts, salicylates, cimicifuga, and colchicin. It is also found in remedies for catarrhal conditions of the mucous mem-

brane, obesity, tumors, congestions of the uterus, liver, etc., and constipation, and it has emetic properties.

The organic constituents of the root have never been fully investigated, but they are reported to include a saponin-like substance, an alkaloid, starch, sugar, formic and other acids. The inorganic constituents amount to over 13 per cent and consist principally of potassium and calcium, probably in the form of formate and oxalate respectively.

The fruit of Phytolacca abyssinica is reported to be a tape-worm expellant.

HYDRANGEA ARBORESCENS. (HYDRANGEACEÆ)

The wild hydrangea or seven barks is an indigenous shrub of the eastern portion of the United States south of southern New York. The root has long been esteemed as a remedy for calculus complaints, and is often present in cystitis mixtures combined with boric or benzoic acid, potassium bicarbonate, buchu, triticum, corn-silk, Viburnum prunifolium, and atropin. It will be found in combination with lithium salts; and with Uva Ursi and matico in elixirs.

An aqueous solution of the alcoholic extract of the drug fluoresces on adding alkali. The presence of a crystalline glucoside, a saponin-like body, a sugar, and resinous constituents have been reported.

A peculiar characteristic of the shrub is the peeling off of the stem bark, which detaches in several successive thin layers of different colors, and which has given rise to the popular name " Seven Barks."

KRAMERIA. RHATANY

Several rhatanies have appeared in the market, and there are three well-recognized commercial species, Peruvian rhatany, the root of Krameria triandra (Krameriaceæ) (Leguminosæ) growing in Peru and Bolivia; Savanilla rhatany, from K. ixina, and possibly other species, growing in Colombia, Brazil, and British Guiana; Para or Brazilian rhatany from K. argentea of Brazil.

Krameria has been used in a multitude of ailments, but is nowhere common. It owes its chief value to its astringency, though it is likewise slightly tonic. It is employed internally in menorrhagia, passive hemorrhages, chronic diarrhea, mucous discharges, leucorrhea; locally for piles, anal fissure, and prolapsus ani, and as a styptic in oral hemorrhage of surface bleeding. In pills it will be found combined with cubeb and ferrous sulphate; with bismuth salts, opium, and licorice; in capsules with copaiba and cubeb; and in pile ointments with sulphur, zinc oxide, resorcin, stramonium, tannic acid, and oil of cade.

The Para rhatany closely resembles the Savanilla variety. The drug contains from 8–20 per cent of tannic acid or a tannin-like substance

giving a dark-green color with ferric salts. Starch, sugar, and calcium oxalate are also present.

Krameria lanceolate of the Southern United States furnishes the Texas krameria, and K. cistoides of Chile is the source of the Payta krameria. The root of Leea speciosa (Vitaceæ) has been used as a substitute drug.

The tincture of Savanilla rhatany forms a clear solution with water, which gives, with alcoholic lead acetate, a purplish precipitate and a colorless filtrate. The tincture of Peruvian rhatany gives a cloudy mixture with water, and a reddish-brown precipitate with alcoholic lead acetate with a light-brown filtrate.

HAMAMELIS VIRGINIANA. WITCH HAZEL

Distilled extract of Hamamelis virginiana (Hamamelidaceæ) is a household remedy for inflammatory conditions, sprains and bruises.

The distilled extract is prepared both from the leaves and the bark which are macerated with alcohol of from 6–10 per cent strength and then subjected to distillation.

A concentrated extract of the drug, representing the resinous portion, is called Hamamelin. This is considered of value as a remedy for piles, and may occur in ointments intended for this trouble. The extract is sometimes used in pill mixtures recommended for disorders of the female genito-urinary tract, and may be combined with hydrastin, Hyoscyamus, opium, Senecio, tannin, thymol, Chamalerium luteum, salicylic acid, boric acid, alum, and eucalyptol.

The distilled extract is combined with glycerin, boric acid, and mucilage of Irish moss in lotions and jellies for sunburn, freckles, and inflammatory conditions of the skin.

TRIFOLIUM PRATENSE. RED CLOVER

Red clover blossoms of T. pratense and T. incarnatum (Fabaceæ) are employed medicinally in alterative mixtures for scrofula and secondary syphilis, in whooping cough remedies, and for washing ulcers. In alterative preparations the drug is combined with others of similar repute such as Stillingia, Xanthoxylum, Lappa, Phytolacca, Iris versicolor, Berberis aquifolium, Cascara amagra, Smilax species, and potassium iodide.

The flowering tops of T. pratense ordinarily furnish the drug known as red clover blossom. The blossom is well known and needs no description. It is the red, purple, or meadow clover.

Power and Salway [1] reported the following summary of a chemical investigation made on this drug. An essential oil distilled from the alcoholic extract contained furfuraldehyde. The water-soluble portion of the

[1] Chem. Soc. Trans., 1910, 97, 231.

alcoholic extract contained considerable sugar, yielding *d*-phenylglucosazone; salicylic and *p*-cumaric acid; iso-rhamnetin; a number of new phenolic substances; pratol, $C_{15}H_8O_2(OH)(OCH_3)$, melting 253° C.; pratensol, $C_{17}H_9O_2(OH)_3$, melting 225°; a substance, $C_{14}H_{12}O_6$, melting 214°; the following glucosides—trifolin, $C_{22}H_{22}O_{11}\cdot H_2O$, melting 260°, which yielded on hydrolysis a yellow coloring matter trifolitin, $C_{16}H_{10}O_6$, melting 275°, and rhamnose, $C_6H_{12}O_5$; isotrifolin, $C_{22}H_{22}O_{11}$, melting 250°; and quercetin, melting 235°.

The portion of the alcoholic extract insoluble in water was chiefly resinous material. The following substances were obtained from it: myricyl alcohol; heptacosane; hentriacontane; sitosterol, $C_{27}H_{46}O$, melting 135–136° $(\alpha)_D = -34.4°$ in chloroform; trifolianol, $C_{21}H_{34}O_2(OH)_2$, melting 295°; a dihydric alcohol; a mixture of fatty acids, chiefly palmitic, stearic, and linolic, and a small amount of pratol.

The tops of T. incarnatum, the crimson, carnation, French or Italian clover, are terminal, oblong or ovoid 1–2½ inches long; flowers sessile ⅓–½ inch long, calyx hairy, corolla crimson, equaling or exceeding the subulata plumose calyx-lobes.

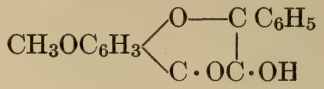
Rogerson [1] examined the flowering tops of the plant and obtained a small quantity of an essential oil, and in the aqueous solution of the alcoholic extract there were present a sugar yielding *d*-phenylglucosazone, benzoic, and salicylic acids, pratol, quercetin, and a new glucoside, incarnatrin, $C_{21}H_{20}O_{12}3H_2O$, melting 242–245°. The portion of the alcoholic extract insoluble in water consisted of a green resin, amounting to 4 per cent of the dried tops, from which were isolated incarnatyl alcohol, $C_{34}H_{69}OH$, melting 72–74°; hentriacontane; a phytosterol, $C_{27}H_{46}O$, melting 135–136° $(\alpha)_D = -41.7°$ in chloroform; trifolianol, and a mixture of fatty acids.

Pratol

This phenol, together with other substances, is removed by ether from an aqueous decoction of the alcoholic extract of the drug. On evaporating the ether and subsequently treating the residue with insufficient ether to bring it entirely into solution, the pratol is left undissolved. It crystallizes from alcohol in needles, having a talon-like shape with curved edges. It is moderately soluble in hot alcohol but only sparingly in water, ether, chloroform, and benzene. It dissolves readily in hot aqueous sodium carbonate and hydroxide, yielding pale-yellow solutions. When dissolved in acetic anhydride and a drop of sulphuric acid added, a yellow coloration is produced. With ferric chloride no appreciable change in color is produced.

[1] Chem. Soc. Trans., 1910, 97, 1004.

Power and Salway state that pratol is isomeric with several flavone derivatives such as the 2-methoxy and 3-methoxy-flavonol



Its general behavior is similar to that of the above-mentioned substance, and it may represent one of the many hydroxymethoxy-flavones which are theoretically possible.

Pratensol

This phenolic substance goes into ether with comparative ease, and may be removed therefrom by alkali carbonates. It is readily soluble in alcohol and acetic acid, but only sparingly in water, chloroform, and benzene. Its alcoholic solution gives with ferric chloride a greenish-black coloration.

Trifolin

Trifolin gradually separates from the aqueous decoction of the alcoholic extract of the drug. On purification by repeated crystallization from aqueous pyridin it crystallizes in pale-yellow needles, which melt with decomposition at 260°. The water of crystallization is expelled at 115°, but on exposure to the atmosphere this is reabsorbed. It is insoluble in cold water, chloroform, benzene, and ether. It is sparingly soluble in alcohol, but dissolves with ease in pyridin. With aqueous sodium carbonate and hydroxide it gives intensely yellow solutions. It dissolves in concentrated sulphuric acid to a yellow solution which rapidly develops a green fluorescense. In alcoholic solution it gives with ferric chloride a dark-brown color.

When trifolin is hydrolyzed by sulphuric acid in alcoholic solution, it is resolved into trifolitin and rhamnose.

$$C_{22}H_{22}O_{11} = C_{16}H_{10}O_6 + C_6H_{12}O_5$$

Trifolitin separates, after distilling off the alcohol, as a yellow precipitate, readily soluble in alcohol and glacial acetic acid, but only very sparingly soluble in ether, chloroform, and benzol. It dissolves in alkalies with an intense yellow color, and dyes mordanted cotton wool a bright yellow. It is precipitated from its alcoholic solution by lead acetate as an orange-yellow lead salt. Its alcoholic solution gives a dark-green color with ferric chloride.

Isotrifolin

This glucoside is soluble in water and may be removed therefrom by amyl alcohol. It yields the same hydrolytic product as trifolin, but it

is evidently not identical with it. It melts at 250° and is much more soluble. Its general behavior is close to trifolin. It dissolves in alkalies with the formation of a deep-yellow solution, and gives with sulphuric acid a yellow color together with a green fluorescence. In alcoholic solution it gives with ferric chloride a deep-brown color.

Incarnatrin

Incarnatrin, the glucoside of T. incarnatum, is soluble in water and is removed from the aqueous solution of the evaporated alcoholic extract of the drug by amyl alcohol, subsequent to the extraction of the phenols with ether. It hydrolyzes to quercetin and a sugar.

$$C_{21}H_{20}O_{12}+H_2O=C_{15}H_{10}O_7+C_6H_{12}O_6$$

The quercetin is soluble in ether, from which it may be removed by sodium carbonate.

Incarnatrin is hydrolyzed by emulsin. It dissolves slowly in concentrated sulphuric acid with a yellow color and a green fluorescence.

XANTHOXYLUM

The dried bark of Xanthoxylum americanum (Rutaceæ) and of X. Clava-Herculis is official under the general name of Xanthoxylum. The berries are also used to a considerable extent. Both species of Prickly ash occur in the eastern portion of the United States, the former being the northern species or Toothache-tree and the latter the southern prickly ash, Hercules Club, or Pepper-wood.

As a drug Xanthoxylum is used as an alterative, stimulant, and sialagogue, and will be found in remedies for rheumatism, toothache, syphilitic and hepatic affections for increasing the secretions, and externally as a counter-irritant.

Some of the liquid combinations which are recommended especially as alteratives or blood purifiers contain in addition to Xanthoxylum, Bicuculla canadensis, Stillingia, Iris versicolor, and potassium iodide; or Trifolium pratense, Arctium lappa, Berberis aquifolium, Stillingia, Phytolacca, Cascara amagra, Bamboo-brier, and potassium iodide; liquid products in which the extract of the berries functionates contain also Stillingia, Bicuculla, Chimaphila, Iris, Sambucus, and coriander. Remedies in tablet form are of the same general type and in addition will be found tonic mixtures containing Cinchona alkaloids, Capsicum, and Cornus florida; ague pills with Cinchona alkaloids, Capsicum, and Gelsemium; and combinations with Cascara sagrada, Belladonna, Nux Vomica, Euonymus, and Capsicum. The powdered bark is chewed as a remedy for toothache and is also combined with Capsicum as a pack for pelvic pains.

There are alkaloidal principles in this drug, but their identity is as yet uncertain. Formerly berberin was considered one of the constituents of the bark, and when chewed the saliva is colored yellow, but later investigation has cast some doubt on the identity of the alkaloid. Jowett and Pyman found canadin and gamma-homochelidonin in X. brachyacanthum, but the chemistry of the Xanthoxylums needs further study.

EUPHORBIA PILULIFERA

Euphorbia pilulifera (Euphorbiaceæ), Queensland asthma herb, is an annual herbaceous plant growing in tropical countries and is reputed to be of value in the treatment of bronchitis, asthma, and other diseases of the respiratory organs. An extract of the entire plant is used in medicine and it is usually combined with iodides, bromides, Lobelia, and nitroglycerin, the combinations being dispensed in tablet and elixir form.

Power and Browning [1] conducted an extensive chemical research on the drug and from the portion of the alcoholic extract which was soluble in water the following substances were isolated; gallic acid; quercetin, $C_{15}H_{10}O_7$; a new phenolic substance; amorphous glucosidic material; a sugar yielding a phenylglucosazone, melting 218–220°, and a trace of alkaloid.

The portion of the alcoholic extract insoluble in water consisted of soft, resinous material amounting to 3.2 per cent of the weight of the crude drug. This resin yielded triacontane, $C_{30}H_{62}$; ceryl alcohol; a new monohydric alcohol euphosterol, $C_{25}H_{39}OH$, melting 274–275°; a phytosterol, melting 132–133°; a phytosterolin (phytosterol glucoside); jambulol, $C_{16}H_3O_4(OH)_5$; melissic, palmitic, oleic, and linolic acids.

About one-half of the resin is soluble in petroleum ether and after separating the solvent, extracting the undissolved portion with ether and separating the latter, the jambulol is obtainable by treatment with hot chloroform, from which it is partly deposited on cooling.

Subsequent to this investigation it has been shown that jambulol is identical with ellagic acid.

STILLINGIA

Stillingia sylvatica (Euphorbiaceæ) is an herbaceous perennial found in dry sandy soil and in pine barrens from Maryland southward, and westward to Kansas and Texas. The root is esteemed for its alterative properties and is a popular component of spring tonics and blood purifiers.

Stillingia will be found in elixirs, syrups, extracts, pills, and tablets combined with one or several of the following drugs: Bicuculla canadensis, Chimaphila, Iris versicolor, Sambucus, Xanthoxylum, Arctium lappa,

[1] Pharm. J., 1913.

Phytolacca, Bamboo-brier, Trifolium pratense, coriander, and potassium iodide.

Stillingia root contains a small quantity of volatile oil and an alkaloid.

KAMALA

Kamala consists of the glands and hairs from the capsules of Mallotus Phillipinensis syn. Rottlera tinctoria (Euphorbiaceæ). The fruit is a roundish, three-valved, three-celled capsule of about the size of a cherry, marked externally with three furrows, and thickly covered with a red powder, which, when separated from the capsules, constitutes the official drug.

It is used principally as a tape-worm expellant combined with aspidium in a medium of olive oil and dispensed in capsule form. The tincture is administered for tape worm, and the ointment for ring worm and parasitic skin diseases.

Kamala is a light, finely granular, very mobile powder of a brownish-red, or madder color, with slight odor or taste but producing an acrid sensation in the mouth and a gritty feeling between the teeth. It is inflammable. It is insoluble in cold and very slightly in boiling water, largely soluble in ether, alcohol and alkalies. The chief constituent of kamala is a resin, the composition of which has not been reported.

The ash of the pure drug should not run over 8 per cent, but in adulterated specimens it may reach as high as 50 per cent or more. Formerly much of the kamala imported was adulterated with sand and reddish earth, but this condition has been improved during recent years.

EUONYMUS ATROPURPUREUS. WAHOO

The root-bark of Euonymus atropurpureus (Celastraceæ), known as burning bush or spindle tree, is employed to a considerable extent medicinally, and is recognized in the National Formulary and British Pharmacopœia. The name "wahoo" is applied indiscriminately to E. atropurpureus and E. americanus, the latter a low or trailing bush having crimson capsules to which the appellation "burning bush" is perhaps more applicable. Both species are used in medicine, but the former only is official.

The extract is often combined with Podophyllum resin in remedies for the liver. It is precribed for intermittent fevers and dyspepsia, and as a laxative, antiperiodic, and tonic. A crude resinous product or concentration, and an alcoholic extract of the drug, are known under the name of "Euonymin," and the term is also applied to a number of substances which at one time or another have been obtained from the bark,

all of which, however, are of indefinite character. Some extracts with a greenish color are obtained from the tree bark, and these appear to be equally active physiologically.

Euonymus extract is dispensed alone in pills, tablets, and elixirs, and in various combinations with Cascara sagrada, belladonna, Capsicum, Nux Vomica, and Xanthoxylum; with Taraxacum, Podophyllum, Apocynum, Eupatorium, Capsicum, and Chelone; with Iris, Podophyllum, and Sanguinaria; and with Podophyllum, ipecac, aloin, and calomel.

Rogerson [1] made a systematic chemical examination of the root bark of E. atropurpureus. An alcoholic extract when distilled with a current of steam yielded a small quantity of a fragrant, yellow volatile oil. The portion of the extract soluble in water, contained a quantity of dulcitol, amounting to about 2 per cent of the weight of the drug; a new acid, $C_5H_4O_3$, melting 121–122°, evidently furan-β-carboxylic acid; a new crystalline alcohol, $C_{21}H_{30}O_4$, melting 248–250°, designated euonymol; a sugar which yielded a *d*-phenyl-glucosone, melting 208–209°, small amounts of tannin and coloring matter.

The portion of the extract insoluble in water consisted of a dark-brown resin which amounted to 3.2 per cent of the weight of the drug. From this resin the following substances were isolated: euonysterol, $C_{31}H_{51}O-OH$, melting 137–138°, $(\alpha)_D - 28.2°$; homoeuonysterol, $C_{40}H_{69}O \cdot OH$, melting 133–134°; atropurol, $C_{27}H_{44}(OH)_2$, melting 283–285°; citrullol, $C_{22}H_{36}O_2(OH)_2$, a substance previously isolated from colocynth; and a mixture of fatty acids consisting of palmitic, cerotic, oleic, and linolic acids.

Citrullol is probably a phytosterol glucoside and it is not unlikely that some of the other substances above mentioned may belong to the same class.

Euonymol is bitter, soluble in alcohol and ether, from which it is not removed by acids or alkalies. If a crystal be dissolved in a small quantity of acetic anhydride and a few drops of concentrated sulphuric acid added, a pink color develops, changing to green with a bronze fluorescence and finally becoming yellow. When dissolved in sulphuric acid it gives a yellow solution with a greenish-yellow fluorescence. When boiled with acetic anhydride and the resulting product recrystallized from ether and ethyl acetate, the acetyl derivative melts 215°.

Euonysterol resembles the phytosterols in its reaction with acetic anhydride and sulphuric acid, but with concentrated sulphuric acid alone a red color is produced. Its acetyl derivative melts 116–118°.

Homoeuonysterol also gives a red color with sulphuric acid. Its acetyl derivative melts 128–130°.

Atropurol gives no color reaction with sulphuric acid alone, but with

[1] Trans. Chem. Soc., 101, 1912, 1040.

acetic anhydride resembles the phytosterols. Its acetyl derivative melts 169–170°.

Furan-β-carboxylic acid is isomeric with pyro-meconic acid. It gives no color with ferric chloride. It is volatile with steam and sublimes 110°.

Previous workers have reported the existence of a well defined glucoside called euonymin, having a physiological action resembling that of the Digitalis glucosides, but Rogerson was unable to confirm this contention.

SUMBUL

Sumbul or Musk Root consists of the dried rhizome and roots of an umbelliferous plant which the U. S. Pharmacopœia designates as Ferula sumbul. There is some doubt as to the identity of the botanical individual yielding the drug which is at present sold on the market.

Sumbul is a nerve stimulant and is combined with Hyoscyamus, Valerian, and Cannabis; with ferrous sulphate, asafetida, and arsenous acid; with the valerianates of iron, zinc, and quinin; with iron, arsenous acid, and strychnin; and with Nux Vomica and Coca.

Heyl and Hart [1] examined commercial musk root and found present a volatile oil amounting to 0.65–1.1 per cent, specific gravity .932 at 15°. This oil on standing deposited a few yellow crystals, melting at 113–114°, but not identified. No sulphur was found.

An alcoholic solution of the drug yielded to water 1.7 per cent sucrose, 1 per cent levulose, acetic acid, betain, and a glucoside of umbelliferone. The portion of the alcoholic extract insoluble in water was of resinous character.

On treating the resin with petroleum ether, there was obtained a considerable proportion of a white acid resin, soluble in 1 per cent potassium hydroxide, and yielding upon hydrolysis vanillic acid and an oil resembling the volatile oil. The petroleum ether portion also yielded a phytosterol, melting 134–135°; an unsaponifiable substance, boiling 168–173°, at 12 mm., the analysis of which indicated the formula, $C_8H_{13}O$; and the following fatty acids from saponification of the glycerides, acetic, butyric, valerianic, tiglic, angelic, oleic, linoleic, cerotic, palmitic, and stearic. On subsequently treating the resin with ether, a phytosterolin, $C_{33}H_{56}O_6$, melting 290° was obtained, also a trace of vanillin, resin esters yielding umbelliferone, and resin acids yielding vanillic acid and umbelliferone on hydrolysis. Chloroform dissolved out a resinous glucoside which gave umbelliferone and glucose upon hydrolysis.

An indication that sumbul is present in a medicinal preparation will be obtained in the regular scheme of analysis when the aqueous decoction of an alcoholic extract is made alkaline. On adding ammonia, for instance,

[1] J. Amer. Chem. Soc., 1916, 432.

a yellowish-green flourescence is produced. This test is not specific as there are other drugs containing umbelliferone, and still others which produce blue or greenish fluorescences with alkalies.

The odor of the drug differs markedly from that of asafetida and the volatile oil contains no sulphur.

COTTON ROOT BARK

Cotton root bark has obtained considerable reputation as an emmenagogue and abortifacient, and is often present in female pills and in secret remedies advertised for restoring the menstrual periods. Some of the combinations containing the drug comprise ergot, aloes, savine, and ferrous sulphate; Cimicifuga, aloes, and ferrous sulphate; ergot, Helleborus niger, aloes, savine, and ferrous sulphate.

Power and Browning [1] investigated the drug from a chemical standpoint. A concentrated alcoholic extract distilled with steam yielded a small quantity of a volatile oil which gave the furfurol color test, and deposited crystals of acetovanillone, melting 112–114°. The portion of the alcoholic solution soluble in water, and the insoluble resin contained a phenolic acid, probably 2–3 dihydroxybenzoic acid melting 196–199°; salicylic acid; a new phenolic substance, $C_9H_{10}O_3$, melting 258–260°; a new yellow phenolic substance, melting 210–212°; betain; a fatty alcohol, $C_{20}H_{42}O$, melting 77.5–78.5°; a phytosterol; a small amount of an hydrocarbon, probably triacontane; ceryl alcohol; oleic and palmitic acids, and a sugar yielding *d*-phenylglucosazone. No tannins nor alkaloids were present.

DAMIANA

The drug damiana has been widely exploited in tonics and tonic beverages, as a remedy for restoring the sexual tone. In medicinal compounds it is usually combined with Nux Vomica or strychnin, phosphorus, zinc phosphide, cantharides, gold, and sodium chloride, and iron salts. Its presence should be suspected in any medicine used as an aphrodisiac.

Tonic beverages which claim to contain damiana have been quite extensively marketed. These products usually bear striking pictorial devices of nude women and men in suggestive attitudes. As a rule the amount of damiana which is present in these mixtures is very small and often it is entirely lacking, and while sometimes the tonic may be fortified with strychnin or phosphorus, it usually consists of a mixture of water and alcohol, sweetened and flavored, and the picture is depended upon to stimulate the sexual activity.

The leaves of more than one species of damiana occur in the trade,

[1] Pharm. J., 1914, 93, 420.

but the true drug is ascribed to Turnera diffusa var. aphrodisiaca, which is described as follows:

Leaves with reddish stems, yellowish flowers and globular capsules may be present. Leaves 25 mm. long, oblanceolate to obovate, margin serrate-dentate, color light green (older leaves somewhat coriaceous and pubescent) odor aromatic, taste somewhat aromatic and bitter.

The chemistry of damiana has never been reported, but it contains a small quantity of a volatile oil which gives the drug and its extract a characteristic odor, a small quantity of a bitter substance and a greenish resin.

In pills, tablets, and elixirs the resin is easily found by evaporating an alcoholic extract of the sample and washing with water. The odor of damiana will then be apparent and the greenish resin left undissolved.

In order to detect the presence of damiana in tonic beverages a sample of 100–200 mils should be evaporated to drive off the alcohol at the same time noting any odor which is evolved and comparing it with that given off by a known extract of authentic damiana previously prepared by the analyst; often a slight characteristic odor will be the only thing that will indicate that damiana was ever used in making up the mixture. The residue is then transferred to a separator, rendered slightly acid if necessary and shaken out with Prolius mixture. The solvent is filtered, evaporated to dryness, the residue treated with warm water and the water decanted. If there is any resin present, it will be left in the residue and it may be treated with alcohol, collected in a small area, and the solvent carefully evaporated to prevent spreading. Damiana resin is of a deep dull-green color with a characteristic odor and is the most marked constituent of the drug.

ASCLEPIAS TUBEROSA. PLEURISY ROOT

The root of Asclepias tuberosa (Asclepiadaceæ), butterfly weed, or orange milk weed is the official Pleurisy root or Asclepias. The plant is a very showy perennial and is common all over the East and in the Southwest, through Texas and Arizona. It differs from the other species of milkweed in having no milky juice in its stem.

Pleurisy root will be found in stomach tonics, and it is also used in affections of the lungs to promote expectoration, to relieve tight breathing and pain in the chest. It will be found combined with opium, camphor, and potassium bitartrate, and the powdered drug is one of the components of a popular remedy for the liquor habit, which includes also Taraxacum, ginger, Capsicum, Angelica and bayberry bark.

The chemistry of the root A. tuberosa has never been definitely determined, but it probably contains considerable starch, and a resin which is

partially soluble in ether. The latter has been called asclepiadin, a glucoside, but there is no evidence to show that it is an individual substance, and in view of our recent knowledge of these resinous bodies it is undoubtedly a mixture.

Some of the other species of Asclepias have been used as medicines. A. verticillata is used in the South as a remedy for snake bites and the stings of venomous insects. A. syriaca is the common milkweed or silkweed, and its root has been employed in asthma and scrofula. A. incarnata, the flesh-colored or swamp milkweed is employed as an emetic and cathartic.

The presence of milkweed roots in mixed liquid products can be detected only by the characteristic bits of vegetable tissue or of starch grains. The drug may occur in certain types of popular remedies mixed with rhubarb or other emodin-bearing drugs, buchu, juniper, aromatic balsams, and sugars, and is recommended for alleviating abnormal conditions of the kidneys and stomach.

ERIODICTYON. YERBA SANTA

Eriodictyon californicum syn. glutinosum (Hydrophyllaceæ), an evergreen shrub of California and Northern Mexio, is the source of the official drug Yerba Santa. The plant is also known as consumptive weed, tar weed, mountain balm, bears weed, and gum bark. It is employed for throat and bronchial affections as a tonic expectorant, and often occurs in preparations containing quinin, for the purpose of obtunding the bitterness of that alkaloid.

The drug contains a considerable amount of resin which is ordinarily insoluble in aqueous menstruum and syrups, and hence would be valueless for admixture with liquid quinin preparations unless prepared with a proportion of alkali sufficient to overcome the precipitation. The presence of an alkaline reaction therefore in quinin mixtures, and the precipitation of resinous matter on adding acid, is a strong indication that Yerba Santa has been used.

In medicines intended for expectorants it is combined with licorice, wild cherry, bromides, tar, Grindelia, salicylic acid, and senega, and it will be found in tablets, syrups, or glycerides.

Power, Tutin, and Clewer [1] have examined the drug and the substances isolated therefrom. They determined that the leaves contain an essential oil, resins, amorphous products, glucose, the hydrocarbons triacontane, and pentatriacontane, formic, acetic, butyric, cerotic, and other acids, both in the free state and as glycerides, a small amount of a phytosterol,

[1] Proc. Am. Pharm. Ass., 1906, 54, 352; Trans. Chem. Soc., 1909, 81; Trans. Chem. Soc., 1910, 97, 2054.

and five new crystalline substances of phenolic character; eriodictyol, $C_{15}H_{12}O_6$, melting 267°; homoeriodictyol, $C_{16}H_{14}O_6$, melting 223°; chrysoeridol, $C_{16}H_{12}O_6$, not melting up to 337°; xanthoeridol, $C_{18}H_{14}O_7$, melting 258°, and eriodonol, $C_{19}H_{18}O_7+H_2O$, melting 199°, and when anhydrous, melting 209°. No alkaloidal substance was present.

The total amount of crude resinous material in the leaves amounts to 29–30 per cent, about 75 per cent of which is soluble in ether. The crude resin has an odor suggestive of tolu.

The phenolic bodies are the characteristic ingredients of Eriodictyon, and are found both on the resinous portions and in the aqueous decoction of the evaporated alcoholic extract of the drug. When the evaporated alcoholic extract is treated with boiling water, the aqueous solution contains eriodictyol, with a suspension of homoeriodictyol, which appears as a yellow solid on cooling. Further quantities of the latter substance with some of the former and the three other homologues are subsequently found in the resin.

The aqueous solution obtained as above mentioned, after filtering from the separated homoeriodictyol, is shaken with ether which dissolves the eriodictyol, and the latter may then be extracted from the ether by a saturated solution of sodium carbonate, previously washing the ether solution with ammonium carbonate to remove resinous matter. On acidulating the alkaline solution and shaking with ether, the phenolic body dissolves and on evaporating the solvent it will be left as a yellow varnish, yielding pure fawn-like crystals on recrystallizing from hot alcohol, after shaking with animal charcoal. The alkaline solution must be at once acidulated as the solution rapidly turns brown when exposed to the air.

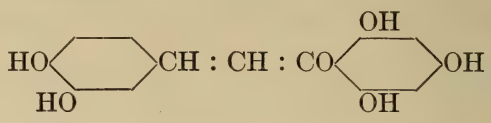
Power and Clewer in their work fractionated the resin by repeated extractions with sodium carbonate, and thus obtained the several high-melting phenolic substances above mentioned. The resin was first extracted with petroleum ether to remove the acid and hydrocarbon constituents and the residue treated with ether. The etheral solution after washing with ammonium carbonate, was extracted with 34 successive portions of 5 per cent sodium carbonate. For each of the first 15 fractions, 20 mils of the solution was employed, for each of the next 10, 50 mil portions, and for the remainder 100-mil quantities. The first and last fractions yielded only resinous matter, fractions 2–13 yielded xanthoeridol, 4–26 eriodictyol, 15–26 chrysoeridol, and 27–33 eriodonol. Homoeriodictyol separated as a sodium compound, which was collected on a filter, washed with ether and a little water and then recrystallized from water.

The procedure adopted by these chemists for the separation of the constituents of Eriodictyon has been detailed here in order to point out to the analyst of an unknown mixture, a method for determining the presence

of this drug. The systematic examination of a liquid or solid medicinal compound according to the qualitative scheme of analysis which is recommended for such mixtures, will furnish an aqueous solution and a residue of resinous character which can be adapted to the tests of Power and Clewer.

Eriodictyol

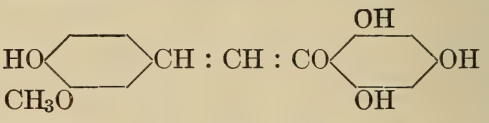
Tutin has determined that this substance is 2 : 4 : 6-trihydroxyphenyl 3 : 4-dihydroxystyryl ketone



It forms fawn-colored plates from glacial acetic acid, darkening and melting to a red liquid at 267° C., moderately soluble in hot alcohol and acetic acid, very sparingly soluble in boiling water and insoluble or very sparingly so in the other organic solvents. It dissolves readily in alkali carbonates and hydroxides, the solutions rapidly absorbing oxygen and becoming deep brown. Ferric chloride gives a deep greenish-brown color rapidly changing to pure brown, when added to an alcoholic or aqueous solution. Its saturated aqueous solution does not reduce Fehling's solution, is not appreciably precipitated by normal lead acetate, but with basic lead acetate it affords a bulky yellow precipitate. Its acetyl derivative melts 195–196°. On hydrolysis with acids it yields phloroglucinol.

Homoeriodictyol

(2 : 4 : 6-trihydroxyphenyl-4-hydroxy-3-methoxystyryl ketone.)



Homoeriodictyol is the monomethyl ether of eriodictyol, and is readily obtained in a pure condition by dissolving in ether and shaking with sodium carbonate when a sodium derivative of homoeriodictyol separates, which may be recrystallized from water, and then decomposed by dissolving in hot water and adding dilute acetic acid. It crystallizes from 70 per cent acetic acid in lemon yellow plates, melting 223°. It is very sparingly soluble in water, but more readily in alcohol and acetic acid than eriodictyol. It dissolves in alkalies with a bright yellow color. Its alcoholic solution gives an intense red-brown color with ferric chloride. Its aqueous solution is not precipitated by either of the lead acetates. No crystalline acetyl or benzoyl derivatives have been prepared. It possesses a

very slight sweet taste. On hydrolysis it yields ferulic (4-hydroxy-3-methoxy cinnamic acid) and phloroglucinol.

This body appears to occur in considerably greater amount than any of the other phenolic compounds, Power and Tutin reporting the presence of 3 per cent. It is isomeric with hesperitin, which is obtained by the hydrolysis of the glucoside hesperidin, a constituent of the peel of the orange, lemon, and other related fruits. Hesperitin crystallizes in colorless needles, melting 226°, soluble in alkalies to a faint-yellow solution, and possessing a sweet taste. It yields isoferulic (3-hydroxy-4-methoxy cinnamic acid) and phlorogulcinol on hydrolysis.

Xanthoeridol, $C_{18}H_{11}O_4(OH)_3$

Xanthoeridol crystallizes from a mixture of ethyl acetate and alcohol in tufts of soft yellow, needles melting 258°. Its solutions in alkalies and concentrated sulphuric acid are yellow, and an alcoholic solution gives a dark-brown color with ferric chloride. Its acetyl derivative when recrystallized from acetic anhydride melts 175–176°.

Chrysoeridol, $C_{16}H_9O_3(OH)_3$

Chrysoeridol is easily separated from eriodictyol, with which it is associated on account of its slight solubility in alcohol. It separates from boiling alcohol in golden-yellow leaflets which do not melt up to 337°. Its color reactions are similar to those of xanthoeridol. Its triacetyl-derivative when crystallized from acetic anhydride melts 211-212°.

Eriodonol, $C_{19}H_{14}O_3(OH)_4$

This substance crystallizes from slightly diluted alcohol in pale yellow needles containing one molecule of water melting 199°. When heated at 110° the water is expelled and the anhydrous body melts 209°. It is readily soluble in ethyl acetate, absolute ethyl, and methyl alcohols. When treated with concentrated sulphuric acid, the crystals become orange and dissolve to a yellow solution with a slight fluorescence. It gives a dark purplish-brown color with ferric chloride. Its solutions in alkalies are bright yellow. It yields iodoform when warmed with iodin and sodium carbonate, differing in this respect from the two substances previously described. It dyes linen mordanted with alumina or iron, bright yellow or dark brown respectively, and is thus similar to the tetramethyl ether of quercetin. It forms a tetracetyl derivative, melting 131°.

PICHI

Pichi is the dried leafy twigs of Fabiana imbricata (Solanaceæ), a shrub with small scale-like leaves, indigenous to Chile. It contains a volatile oil, a bitter alkaloid, resin, and a substance resembling æsculin.

Pichi will be found in diuretic mixtures combined with corn-silk and triticum.

An aqueous liquid obtained by washing an evaporated alcoholic extract of pichi shows a pink fluorescence when acidulated. The color turns blue on adding ammonia, the fluorescence persisting.

The resinous portion of the drug contains a resene which is soluble in ether and may be sublimed. The resene obtained in this way gives a yellow color with concentrated sulphuric acid, becoming red on warming. When dissolved in carbolic acid, treated with zinc chloride and warmed, a yellow-brown color is obtained; on adding concentrated sulphuric acid, a rose-red color appears, soon changing to purple.

COLLINSONIA CANADENSIS. STONEROOT

Collinsonia canadensis (Labiatæ), horse or ox-balm, citronella or rich-weed, a perennial aromatic herb growing in moist woods in the eastern and central portions of this country, furnishes the drug known as stone-root.

Stoneroot is diuretic, alterative, and tonic to mucous tissues, and is employed in chronic catarrhal affections of the stomach and genital organs. It will be found in elixirs combined with Chondrodendron tormentosum, buchu, and juniper berries, and its presence may be suspected in any proprietary remedy intended to alleviate chronic ailments of the kidneys. It is a popular remedy for that condition of the larynx known as " Ministers' Sore Throat."

The flowing top of the green fresh herb has a limited use. The extract of this portion of the plant has a characteristic lemon-like odor and a peculiar aromatic taste.

SCUTELLARIA LATERIFLORA. SCULLCAP

The perennial herb, Scutellaria lateriflora (Labiatæ) is the official Scullcap. There are several other species of Scutellaria and some of them no doubt are occasionally mixed and sold with the official drug.

The drug was formerly held in great repute as a remedy for hydrophobia, but its use for this disease has been largely abandoned, and it is now employed as a tonic, nervine, and antispasmodic, and will be found in remedies for chorea, convulsions, tremors, intermittent fevers, neuralgia, delirium tremens, and nervous affections generally.

It is combined with Cypripedium, hops, and Lactuca canadensis in fluid extract scullcap compound; with Viburnum opulus and skunk cabbage in female nerve remedies of the " Viburnum Compound " type; and in tablets with lupulin, ergot, atropin, and zinc bromide.

There is no research recorded, dealing with the chemistry of S. lateri-

flora. S. altissima, a foreign species, has been studied by Goldschmidt and Zerner,[1] and by Bargellini,[2] who worked on the composition and synthesis of scutellarin, a glucosidal body, which they extracted from the plant. Whether this glucoside exists in S. lateriflora has yet to be determined. The researches of these chemists showed that scutellarin, $C_{21}H_{18}O_{12}$, crystallized in yellow needles. When suspended in water, treated with concentrated sulphuric acid until it dissolved, and then poured into water, scutellarein, $C_{15}H_{10}O_6$, was deposited and glucuronic acid remained in solution. When boiled with 25 per cent potassium hydroxide in a current of oxygen, para-hydroxyacetophenone resulted, and if hydrogen peroxide is added to the alkaline solution, para-hydroxybenzoic acid is formed.

Scutellarein on boiling with aqueous potassium hydroxide, gives para-hydroxyacetophenone and a substance resembling phloroglucinol in its color reaction with a pine splinter. Scutellarein gives the following colors on wool with the mordants mentioned; chromium, reddish brown; aluminum brownish yellow; tin, lemon yellow; iron, olive green.

In dilute alcohol glucuronic acid gives a green color when treated with alpha-naphthol and sulphuric acid; with more water the color changes through blue to violet and even to red. The green color is regenerated by concentrated sulphuric acid. The color reaction previously described for scutellarin is really a reaction for glucuronic acid.

LEPTANDRA

Leptandra or Culver's root is the rhizome and roots of Veronica virginica (Scrophulariaceæ), a plant indigenous to North America. The drug has quite an extended medicinal use, and the crude resinous material obtained therefrom is one of the products to which the name "leptandrin" has been assigned. The term has also been applied to a glucosidal substance reported as occurring in the root, but the existence of such a chemical individual is doubtful. Leptandra is also known as Bowman's root, tall speedwell, and tall veronica.

The drug or its resinous constituents enter into a number of cathartic remedies and liver regulators, and usually will be found combined with Podophyllum resin. The cathartic pills and tablets consist of combinations of Leptandra with aloin, jalap, Podophyllum, gamboge, gentian, Capsicum, Hyoscyamus, colocynth, and oil of peppermint. The liver combinations are of similar composition, but without Hyoscyamus and with the addition of calomel, Veratrum viride, and croton oil. Some special formulas contain juglans and Sanguinaria; Euonymus, creosote, chirata, and Iris versicolor; Leptandra is one of the constituents of the

[1] Monatsch., 31, 439. [2] Gazz. chim. ital., 45, I, 69.

U. S. P. vegetable cathartic pills. It will be found in elixirs with Cascara sagrada, senna, juglans, and Rochelle salt, and in fluid extract mandrake compound with Podophyllum, senna, and jalap.

Power and Rogerson [1] found that the root contained 6–7 per cent of a dark-brown resin, soluble in alcohol, from which they isolated a phytosterol called verosterol, $C_{27}H_{46}O$, melting 135–136°, $(\alpha)_D - 33.0°$, a mixture of fatty acids (oleic, stearic, palmitic, and linolic), *p*-methoxycinnamic and 3 : 4-dimethoxycinnamic acids. The latter substance was also present in considerably larger quantity in an aqueous solution of the alcoholic extract of the drug, together with mannitol, a sugar yielding *d*-phenylglucosazone, melting 209–211°, tannin, coloring matter, and an intensely bitter amorphous substance.

No glucosides were found, and the absence of saponin was established. The fact that an aqueous solution of 3 : 4-dimethoxycinnamic acid froths strongly on agitation, has doubtless led to the recorded statements of the presence of saponin in leptandra.

The identification of Veronica virginica in medicinal mixtures by chemical means is not easy of accomplishment. The isolation of 3 : 4-dimethoxycinnamic acid would point strongly to the presence of the drug, but if "leptandrin," or the resinous portion were used alone, this acid would occur in minute quantity only, and probably would escape detection. The isolation of verastrol from a mixture containing in all probability other phytosterols, would be practically impossible. By centrifuging a portion of the diluted alcoholic extract of the sample, any vegetable tissue present would be concentrated and by careful microscopic examination the characteristic feature of the drug might be detected.

VERONICA OFFICINALIS

The leaves and flowering tops of Veronica officinalis (Scrophulariaceæ) the common speedwell or Paul's betony, are used in the form of an infusion for asthmatic troubles, coughs, and catarrh of the bladder.

MITCHELLA REPENS. SQUAWVINE AND OTHER "SQUAW" DRUGS

The original discovery of the efficacy of many drugs is often ascribed to the Indians, and this fact is featured in the literature of certain classes of proprietary remedies especially of the female regulator, spring tonic, and herbal compound type. For this reason there are several different drug plants to which the significant name of "Squaw" is attached, such as Squawvine, Squaw-weed, Squaw-root, etc.

While there are probably several plants to which the name Squawvine is applied, the drug to which it belongs is Mitchella repens (Rubiaceæ),

[1] Trans. Chem. Soc., 1910, 97, 1944.

the well-known partridge berry, a procumbent evergreen vine of our eastern woods. The entire aerial portion of the plant furnishes the drug.

Mitchella repens is employed in dropsy, suppression of urine, diarrhea, and especially in deranged uterine conditions. Its presence may be suspected in any preparation, elixir, tablet, or ground mixed herb, called a female regulator, mother cordial, viburnum compound or squaw-weed compound. It is usually combined with Viburnum opulus (Cramp bark), Chamælirium luteum (Helonias), Caulophyllum, Aletris farinosa (Star-grass) and Viburnum prunifolium (Black Haw).

A survey of our North American botanical drugs shows the following list of common names suggestive of Indian origin:

Squawhish. Viburnum opulus.

Squawflower. Trillium erectum (Wake-robin, birthroot).

Squawmint. Hedeoma pulegioides (Pennyroyal).

Squawroot. Applied to Caulophyllum thalictroides and Cimicifuga racemosa. (Blue and black cohoshes).

Squaw-weed. Eupatorium ageratoides and several species of Senecio.

Viburnum and the cohoshes have been given separate consideration.

Senecio aureus (Compositæ), the Life-root or Swamp Squaw-weed, is the species of Senecio of importance medicinally. S. Robbinsii is called Robbins Squaw-weed; S. discoideus, Northern Squaw-weed; S. obovatus, Round leaf Squaw-weed; and S. Crawfordii, Crawford's Squaw-weed. S. Aureus is familiar to all in the early spring and summer as the golden ragwort, and is one of the earliest of the Compositæ to bloom. It is another of the numerous drugs which is supposed to have a special influence on the female reproductive organs and will be found in remedies for suppressed menstruation and other abnormal conditions of the uterine system.

The herb and root furnish the drug. The flower resembles the arnica in some respects and the genus is closely related to the Arnicæ.

This plant has been reported as containing alkaloidal constituents, but its chemistry has never been carefully investigated.

THE VIBURNUMS

Several species of Viburnum (Caprifoliaceæ) have furnished drugs reputed of value in the treatment of asthmatic conditions, and for their uterine tonic and sedative effects. For a considerable period the identities of the products sold on the market for true Viburnum, were in a confused state, and hence the descriptions credited to these drugs in the past must in some instances, be taken with reservation.

There appear to be three species of Viburnum recognized as furnishing medicinal drugs. The cramp-bark is the bark of the indigenous shrub

V. opulus, which grows from New Jersey, Michigan, and Oregon northward. The drug known as V. prunifolium is the bark of the root of the black haw, and the bark of the root of V. lentago, the former occuring from Connecticut to Georgia west to Michigan, Kansas and Texas, and the latter having a range from Hudson Bay to Manitoba to New Jersey and along the Alleghenies to Georgia, westward to Indiana, Kansas, and Colorado. V. lentago is the sweet viburnum, sheep- or nanny-berry, V. prunifolium, the stag-bush or slow berry, and V. opulus, the highbush cranberry.

For a number of years and until quite recently the drug sold as cramp bark was not derived from V. opulus at all, but from the mountain maple, Acer spicatum. The drug described in the seventh and eighth revisions of the U. S. P. as V. opulus applies to Acer spicatum. The National Formulary, fourth edition (1916), correctly describes V. opulus.

The reason for the indiscriminate gathering of the barks of the highbush cranberry and mountain maple, is apparent to one familiar with the growing plants. Mountain maple assumes the appearance of a shrub at one stage of its growth, and the structure of its leaves differs from the usual forms of the maples, and in the eyes of the ordinary drug collector might readily be mistaken for Viburnum. One may often see the mountain maple growing side by side with Viburnum, and this condition apparently obtains throughout the range of both species.

V. opulus is a component of many of the mixtures recommended in female complaints of the uterine tract, and is combined with Chamælirium, Caulophyllum, Mitchella, Aletris, Scutellaria, skunk cabbage, and V. prunifolium.

V. prunifolium is combined with the above-mentioned drugs and in other combinations with Hydrastis and Jamaica dogwood (Piscidia,) with Hydrastis, Jamaica dogwood, Cimicifuga, Cascara sagrada, Hyoscyamus, Cannabis sativa, and Potassium bromide; with boric acid, potassium bicarbonate, buchu, Triticum, corn silk, Hydrangea, and atropin; with celery, coca, and kola.

These combinations may be found in liquid, tablet, and capsule form.

Viehoever, Ewing, and Clevenger [1] report the results of a research made with a series of commercial specimens of cramp bark and black haw collected in 1915, and examined as to their identity. Of the fifty samples of cramp bark examined, forty-eight were derived from Acer spicatum. The specimens of the black haw were true to name. In 1916 they examined samples of Viburnum preparations in general on the market and found that those of V. prunifolium were true to label, while nearly all of those supposed to be made from V. opulus contained no Viburnum at all, but gave positive tests for maple.

[1] J. Am. Pharm. Ass., 1918, (7) 944.

There is no difficulty in distinguishing between the Viburnum and Acer barks, both microscopically and chemically. The tannins of the former give a green color or precipitate with freshly prepared iron salts, whereas the tannin of the latter gives a blue precipitate or color.

When working with the crude drug, a cross-section or a small quantity of the powder is treated with a drop of freshly prepared ferrous sulphate (1–1000), and the characteristic colors develop in a few minutes.

Another distinguishing test for maple bark is the red lignin reaction obtained when a drop of phloroglucin-hydrochloric acid (phloroglucin 0.1 gram, alcohol, and concentrated hydrochloric acid 10 mils each) is applied to the inner side of the bark. Any wood fragments attached to the sample must be removed. The test is therefore applicable only in the case of the whole drug and not to ground samples. Viburnum barks yield but a faint reaction if any. When the above described reaction is carried out on Viburnum specimens, the odor of valerianic acid will develop. Acer barks do not yield this acid.

To distinguish between maple and Viburnum tannins in pharmaceutical preparations containing alcohol, about 10 mils are diluted with three volumes of water and shaken out with 15 mils of ether. The ethereal layer is filtered and shaken in a test-tube with an equal volume of water containing two drops of freshly prepared saturated ferrous sulphate solution. A green color in the lower layer indicates a Viburnum species, a blue color indicates a maple.

A confirmatory test for the Viburnum species should be made by separating and identifying valerianic acid. If the sample is a fluid extract 10 mils should be made alkaline with sodium hydroxide and boiled to expel the alcohol; if a mixed pharmaceutical is under examination, a larger quantity should be neutralized with sodium bicarbonate and evaporated to expel the alcohol. The alcohol free mixture is then acidified with sulphuric acid, distilled with steam, and the presence of valerianic sought in the distillate. The acid may be separated from the distillate, by saturating with salt, shaking out with ether, transferring the ethereal solution and removing the solvent over the steam-bath. Viehoever and his coworkers identified valerianic acid by its boiling-point and by the characteristic microchemical forms of the copper, zinc, and mercury salts. The zinc compound prepared with zinc nitrate was the easiest to obtain.

VALERIANA OFFICINALIS

The rhizome and root of Valeriana officinalis (Valerianaceæ), the common valerian, is used as a stimulant to the nervous system, and is a component of medicines used in hysteria, hypochondria, restlessness, and other nervous disorders. Valerian is combined with Hyoscyamus and camphor;

with phosphorus and zinc salts; with Hyoscyamus, musk root (Sumbul), and Cannabis sativa; with coca, codein, Cannabis sativa, strychnin, arsenous acid, and ferrous carbonate; with Sumbul and asafetida; with Sumbul, asafetida, ferrous sulphate, and arsenous acid, etc. These sedative mixtures are usually dispensed in the form of pills and tablets, and are often sold at a high price with great claims as to their virtue in restoring normal sexual functions or for controlling abnormal conditions. The valerianates prepared from valerianic acid are often present in sedative mixtures, and these products as well as the description of valerianic acid have been discussed in the section of Pure Organic Bodies.

The characteristic constituent of the valerian root is the oil which amounts to about 1 per cent, and which contains, among other constituents, the valerianate of borneol. This ester gradually hydrolyzes, and hence the root and the extract have the odor of valerianic acid. The root of Valeriana mexicana yields an oil containing free valerianic acid, and Japanese valerian, which is probably a variety of V. officinalis, yields an oil which closely resembles the oil of the official drug, but which contains the acetate of an alcohol having the composition, $C_{14}H_{24}O_2$, and termed kersyl alcohol. The latter substance crystallizes in large well-formed crystals, melting 85°. It is odorless, insoluble in water, readily soluble in organic solvents, boils 155–156° under 11 mm. pressure, and is lævogyrate.

The odor of valerianic acid is apparent in examining other drugs and their extracts, notably the Viburnum, Angelica, Sambucus species, etc., hence it is necessary to use caution in diagnosing the presence of V. officinalis.

Oil of valerian is a yellowish-green to brownish-yellow liquid, slightly acid, with a penetrating and characteristic and not unpleasant odor. Old oil is dark brown and viscid, with a strongly acid reaction due to the presence of free valerianic, formic, acetic, and butyric acids, often with considerable separated borneol, and having a disagreeable odor. The normal gravity is between .93–.96, $(\alpha)_D = -8$ to $-13°$, acid number 20–50, ester number 80–100, and saponification number 100–150.

BRYONY ROOT

The drug known as bryony root is yielded by the plants Bryonia alba and B. dioica (Cucurbitaceæ). Both of these plants are natives of Europe, but the latter is the species commonly found in England, and is frequently designated English bryony. The roots of both species are considered by some authorities as possessing the same properties, and they appear to be collected and sold as bryony without regard to their botanical individuality. The roots of B. americana and B. africana are respectively used in the West Indies and Africa in cases of dropsy.

Bryony root is an hydrogogue cathartic, and is chiefly employed in dropsy. It is also prescribed to a limited extent in chronic intermittent fever, enlargement of the spleen, chronic bronchitis, and catarrhal whooping cough. It is usually dispensed in the form of tablet triturates and coated tablets. Bronchitis mixtures contain in addition to bryony, aconite, belladonna, tartar emetic, and potassium bichromate; fever combinations include aconite and belladonna; and cold and fever mixtures contain aconite, Eupatorium perfoliatum, Gelsemium, and camphor, monobromate; tonsillitis compounds consist of aconite, belladona, and mercuric iodide, often with the addition of morphin and salicylates. For dropsical conditions the fluid extract or a tablet of the tincture are employed.

Power and Moore [1] examined B. dioica chemically. An enzyme was found which hydrolyzed a glucosidic constituent of the root, and also acted on amygdalin and salicin. An alcoholic extract of the root yielded 2 per cent of a resin and a water soluble portion which contained a colorless, crystalline, neutral substance, $C_{20}H_{30}O_5$, melting 220–222°, slightly soluble in ether and when purified, almost insoluble in ether, but dissolving readily in alcohol. The water-soluble portion also yielded a glucoside, an amorphous alkaloid and a sugar which formed a *d*-phenylglucosone, melting 208–210°. The glucoside was soluble in amyl alcohol and ethyl acetate, bitter, precipitated from aqueous solution by tannin, and giving no color with ferric chloride. On hydrolysis with dilute sulphuric acid, it gave a brown resin and a sugar whose *d*-phenylglucosone melted 208–210°. The alkaloid was intensely bitter, soluble in water and alcohol, but sparingly in ether and chloroform, and was precipitated by the usual alkaloidal reagents and tannin. Ammonia was evolved on heating with alkali hydroxide, and hydrochloric acid decomposed it with the formation of ammonium salt.

The resin was dark brown, viscous, and completely soluble in ether. From it were isolated a phytosterol, $C_{27}H_{46}O$, melting 137° and optically inactive; bryonol, melting 210–212°, and a mixture of oleic, linolic, palmitic, and stearic acids. Bryonol belongs to the group of substances which Power and Salway have since concluded are phytosterol glucosides. Its solution in chloroform gave with acetic anhydride a series of color reactions similar to those produced by ipurganol, a purplish pink, changing to blue, green, and brown, and it dissolved in concentrated sulphuric acid with a yellow color, the solution showing a green fluorescence. It is closely allied to cucurbitol, a substance isolated from the resin of watermelon seed.

The substance obtained from bryony root by precipitation with tannin, and designated " bryonin " by previous investigators, is evidently a complex mixture.

[1] Trans. Chem. Soc., 1911, 99, 937.

PUMPKIN SEED

The seeds of the common pumpkin, Cucurbita pepo (Cucurbitaceæ), have attained considerable reputation for their tænicidal properties. The fluid extract is used for expelling tape-worm and in combination with Cascara, senna, Rochelle salt, Chenopodium, and sodium bicarbonate it is prescribed as a children's remedy.

Power and Salway [1] determined that the seeds contained about 34–35 per cent of a fixed oil removable by petroleum ether, consisting of the glycerides of linolic, oleic, palmitic, and stearic acids; a resin amounting to about 0.5 per cent; a small amount of salicylic acid; soluble proteins, sugar, and starch. Neither the oil nor the resin was found to effect the complete removal of tape-worm which was administered under the usual conditions of fasting and followed by a dose of castor oil.

TARAXACUM

The root of the well-known dandelion, Taraxacum officinale syn. T. taraxacum (Cichoriaceæ), is a popular tonic and alterative. It is chiefly employed in derangements of the liver, in dyspepsia, in cutaneous eruption due to a disordered liver, and of late has been prescribed as an adjunct to the treatment of cancer.

It is combined with senna; with Podophyllum and Conium; and with Sarsaparilla; with licorice and wild cherry; with licorice, gentian, yerba santa, and Eucalyptus, etc., in liquid extracts and elixirs. In pills and tablets extract of Taraxacum is combined with quinin, arsenous acid, and iron; with podophyllum resin, Capsicum, Euonymus, Apocynum and balmony; with Nux Vomica, colocynth comp., quinin, oxgall, and pancreatin and other similar combinations.

Powered Taraxacum occurs mixed with Asclepias tuberosa, Ginger, Capsicum, Angelica, and Bayberry bark in a mixture designed as a secret remedy for intoxication and the drink habit.

The plant grows all over the United States, but the drug is chiefly imported from Europe.

Dandelion root contains considerable inulin and a lævorotatory sugar which appears to be mostly lævulose. Power and Browning [2] found that an alcoholic extract of the drug yielded a resin and certain water-soluble substances, including *p*-hydroxy-phenylacetic acid, melting 144–146°; 3 : 4 dihydroxycinnamic acid, and cholin, $C_5H_{15}NO_2$. The resin amounted to 1.8 per cent of the weight of the dried root and yielded a monohydric alcohol, taraxasterol, $C_{29}H_{47}OH$, melting 221–222°, $(\alpha)_D$+96.3°; a monohydroalcohol homotaraxasterol, $C_{25}H_{39}OH$, melting 163–164°, $(\alpha)_D$+25.3°;

[1] Journal Amer. Chem. Soc., 1910, 32, 346.

[2] Trans. Chem. Soc., 101, 1912, 2411.

cluytianol, $C_{29}H_{46}O(OH)_4$ melting 297° (a phytosterolglucoside); palmitic, cerotic and melissic acids, together with a mixture of unsaturated acids, consisting chiefly of oleic and linolic, with apparently a little linolenic acid.

An extract of Taraxacum root when extracted with Prolius mixture yields a trace of material giving a precipitate with Mayer's reagent.

The alkaloid cholin probably furnishes the best indication of the presence of the drug in medicinal mixtures. If an alcoholic extract is evaporated and treated with water, the cholin will go into the aqueous liquid. After precipitating with basic lead acetate, filtering, and removing the excess of lead with hydrogen sulphide, the filtrate on evaporation may be concentrated to a thick syrup, extracted with alcohol, filtered, the alcoholic solution concentrated and the treatment with alcohol repeated until no insoluble material remains. The alcoholic solution is then treated with a saturated solution of mercuric chloride in alcohol and allowed to stand several days. The precipitated cholin compound is then filtered, washed with alcohol, and dissolved as completely as possible in water, from which the mercury is precipitated with hydrogen sulphide. The filtered liquid, is neutralized with sodium carbonate, slightly acidified with hydrochloric acid, and evaporated to dryness in a vacuum desiccator. The dry residue is treated with absolute alcohol, filtered, evaporated, and the treatment with absolute alcohol continued until the inorganic salt is eliminated. The final product will be deliquescent and its aqueous solution gives a yellow precipitate with gold chloride. Its solution in absolute alcohol will give a precipitate with platinic chloride, which if dissolved in a little water will finally deposit in the form of reddish-brown plates, melting with decomposition at 250–254°.

It is probable that cholin is the substance to which the name "taraxacin" was given by investigators who have, at one time and another, attempted to determine the constituents of Taraxacum.

BURDOCK. ARCTIUM LAPPA

Burdock root is a popular alterative. Its extract is employed in remedies intended for gout, rheumatism, leprosy, and similar diseases. It usually occurs in admixture with other drugs, especially Stillingia, Phytolacca, Xanthoxylum, red clover, and Iris. Mixtures of the Succus Alterans or Alterative compound type consist of bamboo-brier root, burdock, Xanthoxylum, Stillingia, and Phytolacca; those of the Trifolium compound order contain red clover, burdock, Berberis aquifolium, Xanthoxylum, Stillingia, Phytolacca, Cascara amagra, and potassium iodide. These preparations are offered in the form of extracts, syrups, pills, and tablets. Sassafras is often present in syrups of burdock root.

The seed is used as a tonic and alterative and has been used successfully in skin diseases, such as psoriasis. The fresh leaves have also a limited use.

The roots of other species of Arctium are also used and are recognized in the U. S. Pharmacopœia. It is directed that the drug be collected from plants of the first year's growth. The flowers are not produced until the second year.

Very little work has been done on burdock root, but it apparently contains a sugar, inulin, and a fixed oil.

GRINDELIA SPECIES. GUM PLANT OR TAR-WEED

There are some thirty species of Grindelia (Compositæ) native of western North America, Peru, and Chile. About seventeen species occur in the western and southwestern parts of North America, G. squarrosa and G. lanceolata extending their range also east of the Mississippi.

G. squarrosa occurs over a wide area, being found in dry soil in Illinois and Minnesota to Manitoba, Missouri, Texas, Arizona, and Mexico, and adventive in southern New Jersey, Pennsylvania, and New York.

The plants furnishing the drug are commonly designated as the above and G. robusta, but it is probable that the botanical identities of the commercial products have been confused with other species.

G. robusta is a somewhat rare plant and according to Perredes [1] occurs much too sparingly to be a factor of any importance in the consideration of the drug on the market. G. squarrosa appears to occur to a limited extent in California, from which State a large part of the commercial drug is obtained.

G. camporum occurs abundantly in the inner coast ranges, in the foothills of the Sierra Nevada, and is almost the only plant found on the plains in certain regions of the Sacramento Valley. G. cuneifolia is the next most abundant species in California, but G. camporum is the common "gum plant" of California.

It is stated that when collectors are asked to furnish separately "Grindelia squarrosa" and "Grindelia robusta," the plant growing in the marshes (G. cuneifolia and its variety paludosa) is supplied for the latter, while G. camporum, the plant of the dry hills and plains is supplied for the former.

The drug commonly occurring on the market is now probably largely G. camporum.

Grindelia is used in the treatment of asthma, bronchial troubles, pertussis, catarrh of the bladder, and other diseases of the mucous membrane of the genito-urinary organs. Locally its tincture or fluid extract

[1] Proc. A. Pha. A., 1906, 54, 370.

has proven of value in ivy poisoning. Fluid extract Grindelia compound contains senna and rhubarb. Bronchial mixtures will contain Grindelia, Eriodictyon, licorice, tar, wild cherry, salicylic acid, and potassium bromide in syrupy or glycerin menstruums. Expectorant tablets contain senega, Grindelia, aconite, squill, guaiac, ammonium bromide, and carbonate. Alkaline extracts of the drug are commonly sold for admixture with syrup without precipitation of the resin.

Power and Tutin [1] found that G. camporum contained 21–22 per cent of a complex resin to which its medicinal value is probably due. This resin was partly soluble in petroleum ether, and the portion remaining undissolved was nearly all taken up by ether, the first fraction being a soft, sticky, greenish mass, and the second a dark-colored resin.

That portion of the Grindelia resins which were soluble in petroleum ether consisted to a large extent of a complex mixture of liquid acids, which were for the most part optically active, unsaturated cyclic compounds, some being oxyacids with apparently benzene nuclei. A very small amount of cerotic acid and apparently a trace of palmitic acid were present. A considerable quantity of chlorophyll was also present. The non-acidic portion of this fraction contained hentriacontane, $C_{31}H_{64}$, melting 68°, a new phytosterol, melting 166°, giving with sulphuric acid in a solution of chloroform and acetic anhydride, a rose color changing to violet, blue, dark green, and finally brown. It consisted, however, for the most part of a complex mixture of esters, presumably glycerides, the acids of which appeared to be similar to those which were present in the free state.

The ether extract of the resin consisted to a very large extent of a mixture of amorphous products, but there were also present very small amounts of grindelol, a colorless crystalline substance, $C_{23}H_{38}O_4$, melting 256–257°, probably a phytosterol glucoside, and a yellow phenolic substance, $C_{14}H_{12}O_5$, melting 227–228°.

That portion of the total resin insoluble in petroleum ether and ether amount to about 8 per cent and was nearly all dissolved by alcohol.

An aqueous solution of an evaporated alcoholic extract of the drug contained free formic and butyric acids, tannin-like substances, *l*-glucose, and protein. It gave precipitates with both neutral and basic lead acetates. No alkaloids nor saponins were detected.

The characteristic odor of Grindelia is due to a volatile oil, and the presence of this ingredient is about the only distinguishing feature of the drug which can be used for its identification in complex mixtures. This evidence, backed by the identification of the readily detectable formic acid and the presence of a dark-green resin, may be considered as proof of the presence of the drug.

[1] Proc. A. Pha. A., 1905, 53, 193, and 1907.

ECHINACEA

The root of the purple cone-flower has been recommended as an alterative and aphrodisiac, and may occur in preparations used for purifying the blood and for toning up the system. It also occurs in remedies intended to reduce swellings, varicose veins and abnormal growths. The freshly scraped root has been employed in the treatment of snake bites.

Echinacea angustifolia (Brauneria a.) Compositæ, the narrow-leaved purple cone-flower is usually considered the source of the drug, but it is probable that the roots of E. purpurea, the purple cone-flower or black sampson, and E. pallida, the pale purple cone-flower, are collected and solid for the official drug without qualification.

It is reported that large quantities of the root of Parthenium integrifolium, prairie dock or American fever-few, have been on the market at various times, apparently intended as a substitute for or adulterant of Echinacea.

Heyl and Staley [1] report the following proximate analyses of angustifolia and purpurea.

E. angustifolia	*Per Cent*	*E. purpurea*
Moisture	10.90	10.18
Starch	absent	absent
Pentosans	15.6, 15.1	15.6
Fiber	24.77, 24.46	29.65, 29.51
Protein	6.54, 6.96	5.31, 5.17
Ash	7.76	6.93
Inulin	5.9	not determined
Inuloid substance	5.94, 6.14	916
	Yield of Extract with:	
Ligroin	0.77	0.93
Ether	1.26, 1.18	1.61
Alcohol	19.7, 19.94	18.28
	Examination of Alcohol Extract:	
Resin	1.84	2.00
Sucrose	6.92	3.40
Reducing Sugars	3.65, 3.52, 3.89	3.41
Volatile Oil	0.04	

No alkaloid sufficiently basic to be extracted by the ordinary methods is present, but the possibility of cholin or allied substances is not excluded.

ARNICA MONTANA

The flowers and the root of Arnica montana (Compositæ) are used medicinally, and a tincture of the flowers is the preparation in common use externally for the relief of pain from bruises, sprains, etc.

[1] Am. J. Pharm., 86, 450.

Arnica flowers are frequently adulterated and substituted by those of Calendula officinalis, Inula species, and Tragopogon pratensis.

CALENDULA OFFICINALIS. MARIGOLD

The ligulate florets of Calendula officinalis (Compositæ) are used for the same purposes as Arnica, and especially as a local remedy after surgical operations. As an internal remedy the drug has little use at present, though it was formerly used as a stimulant and diaphoretic. It will be found in certain popular local remedies intended to allay inflammation and reduce swellings, where it is mixed with Artemisia absinthium, Echinacea angustifolia, menthol, oils of lavender, sassafras, etc.

Calendula contains a volatile oil and a gum which forms a transparent white mucilage with water, not precipitated by tannin.

CARTHAMUS TINCTORIUS. SAFFLOWER

Safflower or American saffron consists of the dried florets of Carthamus tinctorius (Compositæ). As a drug it was formerly employed for the same purposes as Calendula, especially to promote efflorescence in measles and other exanthemata, as a diaphoretic, and to dissipate incipient catarrh and muscular rheumatism. It is used to some extent as a component of emmenagogue mixtures with aloes, rue, and savine.

THE CONDIMENTAL DRUGS

There are several highly flavored vegetable products which are esteemed as flavoring agents in different classes of foods and have also an extended use in the compounding of medicines, where they functionate as flavoring agents, aromatics, or carminatives.

Anise

Anise seed, the fruit of Pimpinella anisum (Umbelliferæ) is used as a carminative, for increasing the secretions of the mammary glands, and as a flavoring agent, in several well-known remedies and official mixtures. Both the ground fruit and the oil are used.

The whole fruit is an important article of commerce, and it is often adulterated with small pebbles, earthy particles specially manufactured for the purpose, the fruits of grasses and rushes, and the fruit of Conium maculatum. The pebbles are easily detected by sprinkling a handful of the sample on the surface of water contained in a large beaker and rapping the sides of the container, when the heavier particles will sink to the bottom. Conium may be detected microscopically, by the mousy odor developed on warming with caustic alkali, and by the examination of an alcoholic extract of the drug for alkaloids. The ash of pure anise amounts to 7–10 per cent. The oil runs from 1.5–6 per cent.

Oil of anise enters into the composition of many different formulæ. Liquid camphor compound contains anise oil, opium, camphor, and benzoic acid; liquid preparations of seneca and Spigelia sometimes contain oil of anise; and it is also present with rhubarb, licorice, and cardamon; and in the sarsaparilla mixtures with sarsaparilla, senna, potassium iodide, licorice, sassafras, and methyl salicylate. Fluid extract of orange compound contains extract of anise seed, orange peel. cloves, caraway, orris root, mace, cinnamon, and tonka.

Oil of anise is present in cough lozenges and tablets, liver pills and infants' corrective tablets.

Fennel

Fennel fruit, from Fœniculum vulgare (Umbelliferæ) and from the variety dulce (sweet or Roman fennel), is a carminative and aromatic drug, and used chiefly as a corrigent of senna, rhubarb, and other unpleasant tasting drugs.

Fennel contains from 2–6.5 per cent of volatile oil, about 12 per cent of fixed oil, calcium oxalate and 7 per cent ash. The volatile oil contains 50–60 per cent of anethol, 20 per cent fenchone, chavicol (an isomer of anethol), anise ketone, anisic aldehyde, anisic acid, *d*-pinene, and dipentine. The oil from sweet fennel contains no fenchone. Macedonian oil contains limonene, and phellandrene but no fenchone.

The drug is adulterated with wheat screenings, undeveloped fruits, and various other umbelliferous fruits and dirt. The sophistications are detected microscopically and by the other tests given under anise.

Oil of fennel is combined with opium and sodium bicarbonate in remedies for the colic of infants. The extract of the seed is one of the components of Warburg tincture.

Caraway

The fruit of Carum carvi (Umbelliferæ) has an extended use as a flavoring agent, and medicinally as a remedy for the flatulent colic of infants.

The most prominent constituent of the drug is the oil, which amounts to 5–7 per cent, and consists of about equal parts of *d*-carvone and *d*-limonene. The ash runs from 5–8 per cent. Calcium oxalate is a constant constituent of the fruit.

Black caraway is the name given to the fruit of two plants belonging to an entirely different family, Nigella sativa and N. damascena (Ranunculaceæ). These seeds contain alkaloidal constituents and a volatile oil with a flavor like the wild strawberry.

Caraway oil is one of the ingredients of fluid extract cardamom compound and of Spigelia and senna compound. It is also a component of

certain pill formulæ with aloes, soap, and confection of roses; rhubarb, colocynth, and Hyoscyamus; gentian, aloes, and rhubarb; aloes, scammony, myrrh, croton oil, and mercury mass.

Coriander

Coriander fruit from Coriandrum sativum (Umbelliferæ), is used medicinally as a stimulant and carminative. The chief use of the fruit is for the preparation of oil of coriander which is an important flavoring agent.

Of the constituents, the most important is the oil, which amounts to 0.5–1 per cent and has a characteristic odor. The normal ash is about 5 per cent. Calcium oxalate is present.

Extract of coriander will be found combined with Stillingia, Chimaphila, Iris versicolor, Bicuculla, Sambucus, and Xanthoxylum berries in syrups and elixirs. It is also combined with senna, jalap, and rhubarb.

Pimento

Allspice or pimento is the fruit of Pimento officinalis (Myrtaceæ). While it is principally used as a condiment, it occurs in medicinal compounds as a stomachic, stimulant, and carminative. It is combined with pepsin, gentian, ginger, cardamom, and cinchona alkaloids.

The fruit contains 3–4 per cent of a volatile oil, which consists of about 60 per cent of eugenol. The ash runs from 4–7 per cent, but according to the standards of the Association of State and National Food and Dairy Departments it should not run over 6 per cent, with not more than 0.5 per cent insoluble in hydrochloric acid. According to the same authorities the crude fiber should run not over 25 per cent, and the quercitannic acid not less than 8 per cent, calculated from the total oxygen absorbed by the aqueous extract. It should be mentioned at this point that determinations of tannins based on the absorption of oxygen are of little value in arriving at a conclusion as to the actual quantity of tannin-like substances present. The most common adulterants of powered allspice are cocoanut shells and cereal starches; other substances reported include clove stems, peas, olive stones, turmeric, pepper, Capsicum, and exhausted ginger.

Tobasco or Mexican allspice is yielded by a variety of P. officinalis; Crown allspice by P. acris.

Cloves

Cloves are the dry undeveloped flowers of Caryophyllus aromaticus (Myrtaceæ), and in the ground state are used for condimental purposes, and in a small way medicinally for their stimulant and antispasmodic effect. The oil of clove is used as a flavoring, a corrective of griping purgatives, and in toothache remedies.

Volatile clove oil, which is the valuable constituent of the flowers, consists of about 70 per cent of eugenol with a smaller quantity of the sesquiterpene caryophyllene. The oil runs from 9–20 per cent. The total ash ought not to be over 8 per cent, the crude fiber 10 per cent, and the food standards of the state officials demand not less than 12 per cent quercitannic acid, determined by the empirical oxygen absorbed method.

Ground cloves are subject to adulteration with clove stems, allspice, starch, exhausted ginger, and the other adulterants common to ground spices.

Oil of cloves is combined with blackberry root bark and cassia and with rhubarb, cassia, and nutmeg. Powdered cloves is one of the ingredients of blackberry cordial, which contains in addition nutmeg and cinnamon. The oil occurs with colocynth, aloes, scammony, and potassium sulphate; with strychnin, pepper, ipecac, and gentian; with aloes, Nux Vomica and Podophyllum resin, and similar combinations in pill formulæ.

Cardamom

The fruit of Elettaria cardamomum (Zingiberaceæ), with its peculiar and characteristic flavor, is added to tonic and stimulant preparations chiefly as a flavoring agent. The commercial varieties are known as Malabar and Mysore cardamoms.

The drug contains 4–5 per cent of volatile oil and from 4–6 per cent ash.

Fluid Cardamom compound contains cardamom, caraway, cassia, and cochineal, and the British formula contains extract of raisin. Cardamom occurs in liquid aloes compound with myrrh, licorice, potassium carbonate, and saffron; in liquid cinchona, rhubarb, and gentian mixtures. Powdered cardamom is one of the ingredients of the compound cathartic vegetable pills and tablets with colocynth, Podophyllum resin, soap, scammony, and aloes; it occurs with gentian, ginger, Pimento, pepsin, and cinchona alkaloids; and with Capsicum and sodium salicylate.

Cassia and Cinnamon

The terms cassia and cinnamon are interchangeable commercially, but strictly speaking cinnamon is the inner bark of Cinnamonum zeylanicum (Lauraceæ) of Ceylon, Sumatra, Java, and tropical Asia, or of C. louriria (Saigon cinnamon), and cassia is the bark of C. cassia, which comes from China, Indo-China and India. Cassia buds are the dry flower buds of the China cassia. Powered cassia often consists of a mixture of several varieties of bark, and the cheaper grades sometimes contain an admixture of the ground buds.

While these products are of economic importance principally as condi-

ments, they have a limited use medicinally as astringents and for their aromatic and flavoring properties.

The ash of the Cinnamonum species should not be over 6.2 per cent. The important constituent is the volatile oil, which runs from 0.5–1 per cent in the Ceylon cinnamon and from .5–3 per cent in the cassia. The oil is composed principally of cinnamic aldehyde. Mannitol is present in the bark.

The powdered drug may be adulterated with the usual spice adulterants, and in addition one may meet with the barks of other trees and epecially those species of Cinnamonium void of aromatic properties.

Batavia cassia or Fagot cassia is the bark of C. burmanii.

Powdered cinnamon is one of the ingredients of aromatic chalk powder, which also contains saffron, nutmeg, cloves, cardamom, and calcium carbonate. The oil and the extract of cinnamon is often found combined with rhubarb and blackberry in liquid preparations. It occurs with aloes and iron sulphate in pills, and with methylene blue, salol, and sandalwood oil in soluble elastic capsules.

CHAPTER XIV

GUMS AND RESINS

Gums and resins have played an important part in medicine since the early ages. To-day many of them are still used to a large extent for their therapeutic value and others are indispensable as mechanical agents. Whether used for the one purpose or the other their recognition is generally important. Gums such as acacia and tragacanth are often employed as emulsifying agents; rubber and colophony furnish the bases of plasters, and the chemist analyzing such preparations with a view to duplication must needs identify the kind and determine, at least approximately, the amount of the mechanical agent present. Nearly all vegetable extracts contain more or less resin or gum, but the resins and gums of a comparatively few species have been described and their character determined. Those that have been investigated are generally extracted from the plant previously to their incorporation into medicine, and therefore they are themselves commercial units, and as such are often the identifying features of the plants. Commercial gums and resins in the powdered form are subject to more or less adulteration and substitution. Standards have been adopted for most of the products recognized by the trade, and of late considerable attention has been directed toward the evolution of reliable tests for determining their quality.

Gums and resins are very different chemically, but they are conveniently considered under one heading and they are very often associated, the one class with the other. Gums belong to a class of complex polysaccharidic glucosides, while resins are composed of esters of aromatic acids with alcohols or resinotannols, resin acids, and indifferent bodies known as resenes. Gums are soluble in or swell up in contact with water and are not dissolved by alcohol. Resins are insoluble or but slightly dissolved in water; most of them are soluble or partly so in alcohol and ether. The resin esters are saponifiable. Naturally occurring mechanical mixtures of gums, resins, and volatile oils are classed as gum resins, oleo-resins, and balsams. Gum resins consist of variable mixtures of gums and resins, often with the presence of volatile oils (aromatic gum resins). Oleo-resins consist of resins and volatile oils, the former frequently being dissolved in the latter. Balsams consist of resins, aromatic acids, alco-

hols, and esters. The terms "gum," "resin," and "balsam" are often applied incorrectly from a chemist's standpoint. Trade customs over many years have brought about this condition, and the confusion of the commercial designation with the true chemical facts will often prove disconcerting to the analyst.

CLASSIFICATION OF GUMS AND RESINS

Gums

Acacia. Soluble in water and precipitated by alcohol.

Irish Moss and Quince Seed Gum. Soluble in water but not precipitated by alcohol.

Agar. Soluble in water and partly precipitated by alcohol.

Tragacanth. Swelling up with water and a portion dissolving.

Indian Gum. Swelling up with water, but not dissolving, yielding acetic acid on hydrolysis with phosphoric acid.

Resinous Substances (Lewton)

True Resins

Copal Group. Insoluble in the usual solvents unless themselves previously fused.

Dammar Group. More or less soluble in ether, chloroform, benzol, and acetone, but insoluble in alcohol.

Sandarach Group. More or less soluble in alcohol. Guaiacum belongs to this group.

Colophony Group. Soluble in alcohol.

Benzoin Group. Soluble in alcohol, liberates benzoic or cinnamic acid when heated.

Shellac Group. Form a turbid solution in alcohol.

Gum Resins

Inodorous Gum Resins. Yield an emulsion with water. Gamboge belongs to this group.

Aromatic Gum Resins. Contain ethereal oils and yield an emulsion with water.

Asafetida Group. Comprises asafetida, galbanum, ammoniacum, and opopanax.

Myrrh Group. Myrrh, clibanum, and bdellium.

Oleo-resins

Varnish Group.

Copaiba Group. Liquids.

Turpentine Groyp. Soft resins, containing larger or smaller quantities of volatile oils.

Elemi Group. Soft resins rarely containing more than 10 per cent of ethereal oil.

True Balsams

Peru balsam, Tolu balsam, and liquid storax.

GUMS

Gums are chemically closely related to the glucosides. O'Sullivan has shown that they are built up of the residues of sugar molecules united by ethereal oxygen to organic acids. The sugars commonly evolved on hydrolysis are galactose and arabinose, but the acids usually differ in different gums, acacia containing arabic acid and tragacanth bassoric acid.

Gums are soluble in, or swell up in contact with water, and are not dissolved by alcohol. They are amorphous, non-volatile, and colloidal. They are not fermentable by yeast. Their solutions are usually lævorotatory, but this is not always the case, as Australian acacia is inactive, and gedda gum is dextro.

They yield mucic acid on treatment with nitric acid.

Natural gums are often admixtures of several gum compounds differing in the number of sugar residues in their molecules. The testing of the gum components of complex mixtures is greatly complicated by the uncertain knowledge of the chemistry of gums and because of the substitution and admixture of one gum with another, often through the ignorance of the crude drug merchant. The trade in powdered gums is large, and opportunities for sophistication are great and often resorted to. These conditions have been the cause of many erroneous reports concerning the chemical reactions and tests of gums. Tests for the presence of tragacanth in ice cream have been worked out on Indian gum of an entirely different composition and properties than tragacanth. Mixtures of Indian gum and acacia have been sold for the pure acacia and used for the same purposes as the pure gum without detection on the part of the user. It is only within the last few years that tests have been devised for successfully proving the admixture of one gum with another. Those tests have been adapted to powdered gums as commercial commodities and not to mixed gums in pharmaceutical combinations such as pills and emulsions. While it is possible to detect an individual gum in a pharmaceutical combination, it is doubtful if one would be justified in attempting to differentiate between several gums when together in such combination unless perhaps the component gums were equally balanced in amount. In such cases the personal experience of the investigator, resulting from the actual knowledge of how authentic gum specimens react, is of greater aid than printed directions.

Acacia Gum (Gum Arabic)

Several species of Acacia (Leguminosæ) yield gums consisting probably of calcium arabate and arabic acid. The gums of the best commercial qualities are designated gum arabic or gum acacia, those of less commercial value are the Senegal gums.

Extensive researches on the sources, chemistry, and economic importance of the Acacia gums have been conducted by the Wellcome Research Laboratories, Gordon Memorial College, Khartoum. The chief gum exported from the Sudan is that obtained in the Kordofan Province from the Acacia verek ('hashab), said to be identical with the Acacia senegal from which senegal gum is derived.

As it ordinarily appears in commerce gum arabic occurs in rounded or ovoid tears or broken angular fragments. The color varies from white or yellowish white to amber. The pieces are usually translucent, but some of the angular fragments are often nearly transparent. When first collected the pieces are transparent and glassy, but on exposure to the sun or artificial heat they dry and crack, the cracked pieces being nearly snow-white in color and very friable. Senegal gum is exposed to a less intense heat, and the gum itself is less brittle, consequently fewer cracked pieces and broken fragments are produced.

The ash of good gum does not amount to over 4 per cent.

The use of these gums for purely medicinal purposes is decidedly limited, being confined to soothing lotions and demulcents. They are important adjuncts in the preparation of pills, compressed tablets, troches, certain kinds of lozenges, and emulsions.

The identification of gum acacia is not difficult. Its quantitative determination is seldom more than approximate. The value of a quantitative determination depends somewhat on the case in hand. If it is a question of accounting for the composition or of closely duplicating a given preparation it is important to know the kind and approximate amount of the gum present.

Gum acacia is soluble in water to a clear liquid but is insoluble in alcohol and other organic solvents and the addition of alcohol to an aqueous solution of the gum precipitates the latter, when the alcohol amounts to 50–60 per cent. Tragacanth mixes with water to a pasty mass and a portion dissolves, but the appearance of the mixture is in no way comparable to that of acacia. Indian gum simply swells up with water to a transparent jelly. If the water is in large amount the mixture appears to be a solution, but it is not.

When a 2 per cent solution of gum acacia is treated with $2\frac{1}{2}$ times its volume of 50 per cent alcohol and a 25 per cent solution of ferric chloride (acid free) is added a precipitate is produced. The deposit is often slow in forming.

Basic lead acetate solution throws out gum arabic as a curdy precipitate. Neutral lead acetate does not produce a precipitate with solutions of the gums usually found in commerce.

Copper sulphate followed by an excess of sodium hydroxide produces a precipitate which rises to the surface and does not dissolve on warming. Dextrin yields a precipitate which dissolves on warming, and the copper is reduced on boiling; however, nearly all samples of acacia have a variable cupric reducing action. The gum can be regenerated by dissolving the copper compound in dilute hydrochloric acid and adding alcohol to throw out the gum.

These tests can be applied directly to a 2 per cent solution of the gum. When working with pharmaceutical mixtures it is advisable to separate the gum from the bulk of the material by digesting the material with water, filtering, and precipitating with an excess of alcohol. The precipitated gum can then be brought on to a filter, washed and dried, and then redissolved in water to a 2 per cent solution.

Emulsions should be mixed with a considerable volume of petroleum ether and then sufficient alcohol added to produce approximately a 50 per cent aqueous menstruum beneath the volatile solvent when this separates. By separating the light solvent which contains most of the oil and treating again, practically all of the oil can be removed. On adding a further quantity of alcohol to the hydroalcoholic layer, the gum ought to separate as a flocculent precipitate and can be tested as above described.

Acacia gum contains an oxydase which causes the production of a blue color when an alcoholic solution of guaiacum is added to a solution of the gum. When a 5 per cent aqueous solution of the gum in cold water is treated with an equal volume of 1 per cent aqueous guaiacol and a drop of hydrogen peroxide added, a brown color develops. These tests may assist in the detection of acacia in the presence of other gums, but it is of no value in testing for it in pharmaceutical mixtures. The oxydase reaction was considered at one time to be limited to, and therefore characteristic of, gum arabic, but recent observations indicate that some of the cheaper grades of Smyrna tragacanths respond to the same tests. Jensen tested authentic specimens of the so-called Indian gums, from Sterculia urens and Cochlospermum gossypium, and obtained no reaction for oxidizing ferments.

Acacia has a saponification value of about 10.

Waters and Tuttle [1] have proposed the following method for the determination of gum arabic:

Fifty grams of copper acetate is dissolved in water, an excess of ammonia added, and the solution diluted to 1000 mils, using water and alcohol in such proportions that the final solution contains 50 per cent

[1] Dept. of Commerce, Bu. of Standards, Technologic Paper No. 67, page 13.

of alcohol. For each determination a 50-mil portion of a gum arabic solution, representing 0.25 gram of gum, is pipetted into a 250-mil beaker, an equal volume of alcohol added, and then 25 mils of the copper reagent, with constant stirring. The precipitate is allowed to settle, is filtered on a tared paper, washed with 50 per cent alcohol containing ammonia, then with 75 per cent, and finally with 95 per cent alcohol. It is dried to constant weight at 105°, ignited in a porcelain crucible, and the ash weighed. The amount of ash is deducted from the weight of the original precipitate and the difference called " net gum arabic." The amount of moisture in the gum originally taken for analysis must be allowed for. This is determined by drying in a current of hydrogen at 105°. No allowance is made for the potassium and calcium, which forms an integral part of the gum. These may be to some extent retained in the precipitate and, therefore, be included in the ash. Any error that may be introduced by neglecting this is small and very much less than the error inherent in the method.

This procedure can be applied to admixtures of gum arabic with tragacanth. The mixed gums should be digested with water, the solution made up to a definite volume, allowed to settle and an aliquot decanted for the determination. The application of this method to mixtures of acacia and Indian gum has not been determined. With dextrin it would apparently work successfully.

If it is proposed to use this method for determining acacia in pharmaceutical mixtures the gum should first be separated, as was recommended in making the qualitative tests.

The gum of the mesquite tree of Texas occurs in tears and somewhat resembles acacia in its physical properties, but it does not yield the characteristic precipitates with lead subacetate and ferric chloride.

Agar Agar

Agar has recently come into prominence as a remedy for constipation. The commercial product consists of the stems of marine algæ, of which the most important are Gelidium corneum, G. cartilagineum, Fucus amylaceus syn. Gracillaria confervoides, Euchema spinosum Ag, and certain species of Tenax and Digartineæ.

Agar occurs in transparent strips of the thickness of straw, or in shorter and thicker yellowish-white pieces, odorless and tasteless. The aqueous solution gives no precipitate with tannic acid (absence of gelatin) and no blue color with iodine. A fragment of the material, however, under the microscope, stained with iodine, will show bluish black in places.

Commercial agar usually contains diatoms, a characteristic form being Arachnoiliscus Ehrenbergii. To obtain the diatoms the organic matter may be oxidized with a mixture of nitric and sulphuric acid. These

diatoms are disk-shaped and from 0.1 to 0.2 mm. in diameter. Spiculæ of sponges are often present.

The characteristic swelling and jellifying properties of agar are due to *d*-galactan or gelose.

C. R. Fellers [1] has recorded an interesting research on agar. The average proximate analysis of a number of samples gave moisture 16.57 per cent, protein 2.34 per cent, nitrogen-free extract 76.15 per cent, ether extract .30 per cent, crude fiber 0.80 per cent, ash 3.85 per cent, silica 0.68 per cent.

The average analysis of agar showed:

	Per Cent		Per Cent
CaO	0.92	As_2O_3	0.000
MgO	0.568	Cl	0.22
Na_2O	0.25	I	Present
K_2O	0.067	Pentosans	3.12
$Fe_2O_3+Al_2O_3$	0.55	Galactan	22.87
SiO_2	0.83	Solution in water, 20°	19.00
SO_3	2.645	Solution in water, 100°	96.20
P_2O_5	0.052	Protein in alcohol precipitate	1.12

Mils excess N/1 HCl, per gram 0.029

The solubility in cold water was determined by placing 5 grams of the air-dried substance in a flask containing 200 mils of water and allowing it to stand for eighteen hours with occasional shaking.

The acidity was determined by treating 5 grams with 250 mils of water, heating until solution had taken place and then titrating 100-mil portions using phenolphthalein.

The relatively high content of sulphur is no doubt due to the practice of bleaching with sulphur dioxide.

The ether extract is an aromatic-scented, light, amber colored, fatty substance of about the consistency of stearin.

A high ash or silica content is indicative of an inferior product.

Agar solutions are partly precipitated or rendered "tacky" with alcohol. Lead subacetate produces a precipitate, but neither lead acetate nor borax causes precipitation.

Irish Moss

Irish moss consists of the fronds of Chondrus crispus and Gigartina mamillosa (Gigartinaceæ), marine growths, which are collected in large quantities. When fresh the color is purplish, but on drying the color disappears in part and as usually found in commerce Irish moss occurs in matted, horny, translucent masses of a yellowish or yellowish-white color.

[1] J. Ind. and Eng. Chem., 1916, 8, 1128.

The mucilage is an important emulsifying agent and is often employed in lotions and jellies. Its presence may be suspected in any product of the type which does not yield a gummy precipitate with alcohol. It is often present in applications for sunburn, chapped hands, chafing, and similar discomforts and in such, aids in distributing the beneficial action of Hamamelis distilled extract, boric acid, and glycerin.

Irish moss softens and becomes gelatinous in cold water and yields a gummy constituent to boiling water. The solution is viscous and jellifies on cooling. It gives no precipitate with gelatin, lead acetate, borax, or alcohol, and is not colored blue by iodin. It gives a precipitate with lead subacetate.

Quince Seed

Quince seed contains a gelatinous substance which is readily soluble in cold water, and mucilage thus produced is a valuable emulsifying agent. It is employed in the preparation of lotions and creams. The seed contains a cyanogenetic glucoside, and under ordinary conditions this passes into the emulsion, and will be apparent through the hydrolysis and liberation of the benzaldehyde and hydrocyanic acid. Quince-seed emulsion is not precipitated by alcohol or borax, but it gives precipitates with lead acetate and subacetate.

Gum Tragasol

Gum Tragasol is the name given to a product obtained as a result of steeping locust-bean kernels with water.

Tragacanth

Tragacanth gum is obtained from shrubs of the Astragalus genus growing principally in Persia and Asia Minor. It enters commerce, as a rule, through ports in Persia, and from there is shipped to Russia, Great Britain, Turkey, India, and the United States. Previous to 1915 large shipments were handled through Hamburg.

The exudations from the gum-bearing species of Astragalus resemble one another closely in physical and chemical characteristics. The whole gum usually occurs in ribbon-like bands or long linear pieces, flattened and often spirally twisted, varying in color from white to light brown. It has a horny appearance and is translucent and opaque when the pieces are dark-colored and thick. The bands are usually marked with ridges.

The composition of the gum is complex. The literature contains the reports of several researches, but it is difficult to coordinate the results. O'Sullivan has determined the presence of starch, cellulose, nitrogenous matter, bassorin, and soluble gum. The soluble gum is built up with complex acids which he terms polyarabinan-trigalactan-geddic acids and

which on hydrolysis yield arabinose. Bassorin, the insoluble portion, is of acid-like character and under the action of excess alkali yields two acids, alpha and beta-tragacanthan-xylan-bassoric acid, the former being readily soluble in water. O'Sullivan found the formula of the alpha acid to be $C_{24}H_{34}O_{20} \cdot H_2O$, and on digestion with 5 per cent sulphuric acid at 98° for twenty minutes it was hydrolyzed to tragacanthose and xylan-bassoric acid; the latter subsequently being resolved into xylose and bassoric acid by 5 per cent sulphuric acid. Bassoric acid is almost insoluble in cold water. It forms a jelly with alcohol.

Tragacanth in the whole condition is recognized without difficulty. The finer grades are white and in thin pieces, the cheaper grades being darker in color and less uniform in appearance, some grades being almost entirely without the ridged and banded structure. The powder is often adulterated. Pure tragacanth when made into mucilage with water yields an opaque mixture which is neutral in reaction, froths when shaken with 5 per cent potassium hydroxide, gives a blue color with iodin and precipitates immediately with 2 volumes of alcohol. When the mucilage is mixed with an equal volume of 2 per cent borax solution no change in consistency is exhibited, and after standing for twenty-four hours it pours out as a homogeneous mixture without stringiness. When boiled with hydrochloric acid the mucilage develops a yellow to brownish tint with separation of a flocculent precipitate. High-grade tragacanth has a saponification value of 140–186. Its ash should not be over 3.5 per cent. It yields from 2–2.5 per cent acetic acid on hydrolysis with mineral acids.

As a remedial agent tragacanth is valuable chiefly as an emollient. It is extensively employed as a mechanical agent in the preparation of emulsions and pills.

It is reported that certain lump tragacanths give reactions for oxidizing ferments which have been attributed to acacia alone. The procedure of the test has been detailed under the description of acacia.

Fromme [1] recommends a method for determining the approximate percentages of acacia and tragacanth when mixed. Two grams of purified sand is placed in a strong test-tube 16×150 mm., with 0.1 gram of the powder to be examined and the contents well mixed by shaking; 1 mil of alcohol is then added, followed by 5 mils of water, and, after shaking well, 20 mils of an ammoniacal solution of copper oxide (cuoxam). The tube is then vigorously shaken and set aside for several hours. A similar test is carried out simultaneously with powdered tragacanth of known purity. On comparing the two tubes the height of the deposit will give a fairly good indication of the percentage of real tragacanth in the sample.

[1] Jahresbericht, Caesar and Lorenz, 1914, p. 28.

The reagent is prepared by shaking copper turnings or powder with 25 per cent ammonia until the solution becomes deep blue.

Berlinia emini gum

The gum from Berlinia emini, indigenous to German East Africa and identified by F. Mannich, resembles tragacanth. It occurs in horny brown opaque pieces with a slight peculiar odor and contains no starch. It yields an acid mucilage which is precipitated by lead acetate.

Indian Gum

There are several gums known as Indian gum, but none of these is obtained from any species of Astragalus. The name *kuteera*, *katirah*, and the same with many other spellings, has been applied to some of the Indian gums and to certain of the Astragalus products, the gums from A. heratensis and A. strobilifera, and it has no special significance and does not indicate the origin or proper classification of the gum. While it is possible that the Indian gum used so extensively in this country may vary as to its origin, the specimens examined in the whole condition correspond with samples of gum Sterculia urens submitted directly from India and from London. Furthermore, in a private report submitted from Bombay it is stated that S. urens is the source of this gum, and that it is used as a substitute for tragacanth in the government hospitals in Bombay.

It occurs in striated irregular lumps, sometimes twisted, transparent or translucent and not in ribbony bands like tragacanth. As it reaches this country it often contains considerable bark which is bolted out before the powdered material is ready for the market. The powder is usually very white, rivaling in appearance that of the best grades of tragacanth. The bark contains characteristic stone cells which pass into the powder, and serve as a means of identifying the source of the product. Tragacanth bark contains no substance of similar character.

The powder of Indian gum forms a nearly transparent jelly with water, swelling up to a considerable bulk and apparently dissolving, though, as a matter of fact, a small portion only is taken into solution. The aqueous solution is decidedly acid to litmus. It is unaffected by iodine solution and does not give a yellow color when warmed with alkali.

When an aqueous mixture of this gum is boiled with dilute hydrochloric acid, a clear solution with a marked pink color results.

Indian gum reacts in a peculiar manner with borax; referred to at some length by Scoville,[1] which property is of value in detecting mixtures. Tragacanth gives a smooth creamy mixture, Indian gum a thick

[1] Druggists' Circular, 1909, 116.

slimy mass, often so gelatinous that it will not pour out of the container, this property being apparent even in presence of considerable amounts of tragacanth. The test is best performed by placing 2 grams of the powder in a 100-mil graduated cylinder, moistening with alcohol and adding about 50 mils water, shaking until a homogeneous mixture is obtained; 2 grams of borax are dissolved in 50 mils of water, added to the jelly, the whole well shaken and allowed to stand overnight. When pure tragacanth alone is under examination, the resulting mixture will pour out of the cylinder without stringing, while if Indian gum is present a stringy mixture results.

Indian gum evolves a relatively large amount of acetic acid when boiled with sulphuric or phosphoric acids. This property furnishes another ready means of detecting, as well as approximately estimating the quantity of the gum present in admixtures with tragacanth. Emery [1] has determined that the average volatile acidity of the gum from S. urens is 15.79 per cent. His procedure for determining the volatile acidity is as follows:

Treat 1 gram of the whole or powdered sample in a 700-mil round-bottomed flask, provided with a long neck, for several hours in the cold with 100 mils of distilled water and 5 mils of sirupy phosphoric acid until the gum is completely swollen. Boil gently two hours in connection with a reflux condenser, whereby a nearly clear, colorless solution is effected. A very small amount of cellulose substance will remain undissolved. Now subject the hydrolyzed product to slow distillation in a vigorous current of steam until the distillate amounts to 600 mils and the acid residue to about 20 mils. This should not be driven too far, however, otherwise there may be danger of scorching the nonvolatile, organic degradation products, with consequent possible contamination of the distillate. It has been found that a spray trap if used in connection with the flask containing the hydrolyzed gum, is effective in preventing traces of phosphoric acid being carried over into the distillate. Titrate with N/10 potassium hydroxide in connection with 10 drops of phenolphthalein solution, finally boiling the liquid under examination until a faint pink color persists. Run a control on same amount of distillate obtained by a parallel operation, with omission of gum, but using like quantities of other ingredients and observing the same conditions as in the test.

The published data on the Indian gums lack coordination. This may be due in part to the uncertainty of the botanical sources of the product. The information thus far obtained refers to two sources, Sterculia urens and Cochlospermum gossypium. The published data on both gums show that the two products are closely allied if not identical in composition.

[1] U. S. Dept. Agri. Bu. Chem. Circ. 94.

Lemeland [1] and later Robinson [2] have conducted researches on a gum which they attribute to C. gossypium, but which is apparently the same as or closely allied to the gum from S. urens. The gum was obtained from a small deciduous tree of Northwestern Himalaya and central India.

An examination of the gum furnished the following results: Moisture, 22.72 per cent; ash, 4.64 per cent; the ash contains iron, calcium, and potassium as oxide and carbonate. 2.04 per cent of the gum is soluble in water, the solution possessing a rotatory power of +77.15°. Determination of the galactans by Tollen's method gave 34.99 per cent (expressed as galactose). No arabinose or sugar other than *d*-galactose could be isolated from the products; 22.59 per cent of pentosans, equivalent to 25.64 per cent of pentoses, was found. The total quantity of sugar could not be determined, owing to the difficulty experienced in hydrolysing the gum, the highest result obtained being less than the sum of the pentose and galactose. On oxidation with nitric acid, 71.8 per cent of mucic acid (on the weight of gum used) was obtained.

The gum examined by Robinson contained 15.5 per cent of water (loss at 100° C.) and 5.2 per cent of ash. It was investigated according to the method proposed by O'Sullivan. It probably consists of the tetra-acetyl derivative of a gummy acid to which the name α-cochlosperminic acid was given. This acid, probably $C_{34}H_{54}O_{30}$, was isolated by treating 100 grams of the gum with 2 liters of 5 per cent sodium hydroxide solution, and after standing for a long time, nearly neutralizing the mucilage with dilute hydrochloric acid, again allowing to stand for a few days, and then adding excess of strong hydrochloric acid solution. The solution was purified by dialysis, and the free gum-acid precipitated by alcohol and a small quantity of hydrochloric acid, washed with alcohol, and dried. It is a white granular substance, having a rotatory power $(\alpha)_D = +57°$; It gelatinizes with water, but does not dissolve. On hydrolysis with dilute sulphuric acid, the gum yields 14.4 per cent of acetic acid, a gum-acid (gondic acid), and two sugars—xylose and hexose, possibly galactose. Gondic acid, $C_{23}H_{36}O_{21}$, is soluble in water and is precipitated from solution by alcohol as a white amorphous substance. It is an anhydride, and has the rotatory power $(\alpha)_D = +97.7$.

RESINS

The main constituents of resins may be divided into the following classes:

1. Resin esters (resins) or their products.
2. Resin acids (resinolic acids).

[1] J. Pharm. Chim., 1904, 20, 253.
[2] Chem. Soc. Trans., 1906, 89, 1496.

3. Resenes, indifferent bodies of unknown classification.

The aroma of resins is due in part to ethereal oils and liquid esters, among which cinnamic acid esters are important.

1. Resin Esters

The resin esters and resins are composed of aromatic acids of the benzoic and cinnamic series and resin alcohols (resinols and resinotannols). Succinic acid, an aliphatic acid, occurs in amber.

a. Benzoic acid, C_6H_3COOH, (Peru and Tolu balsams, Siam benzoin, dragon's blood)

Benzoylacetic acid, $CH_2(C_6H_5CO)COOH$, (Dragon's blood)

Salicylic acid, $C_6H_4\begin{cases}OH\\COOH\end{cases}$ (Ammoniacum)

b. Cinnamic acid, $C_6H_5CH{=}CHCOOH$ (Peru and Tolu balsams, Storax, Sumatra benzoin)

P-cumaric acid, $C_6H_4\begin{cases}OH\\CH{=}CHCOOH\end{cases}$ (Aloes)

Ferulaic acid, $C_6H_3\begin{cases}OH & (1)\\OCH_3 & (2)\\CH{=}CHCOOH & (4)\end{cases}$ (Asafetida)

Umbellic acid, $C_6H_3\begin{cases}OH & (1)\\OH & (3)\\CH{=}CHCOOH & (4)\end{cases}$ with its anhydride

Umbelliferone (Asafetida, Galbanum)

Resin Alcohols. Resinols do not give a tannin reaction. Resinotannols are colored by iron salts.

Resinols.

Succinoresinol, $C_{12}H_{20}O$	(Amber)
Storesinol,	(Storax)
Benzoresinol, $C_{16}H_{25}(OH)O$	(Benzoin)
Chironol, $C_{28}H_{47}OH$	(Opopanax)

Resinotannols.

Siaresinotannol, $C_{12}H_{13}O_2(OH)$	(Siam benzoin)
Sumaresinotannol, $C_{18}H_{19}O_3(OH)$	(Sumatra benzoin)
Peruresinotannol, $C_{18}H_{19}O_4(OH)$	(Peru balsam)
Toluresinotannol, $C_{17}H_{17}O_4(OH)$	(Tolu balsam)
Galbaresinotannol, $C_{18}H_{29}O_2(OH)$	(Galbanum)
Ammoresinotannol, $C_{18}H_{29}O_2(OH)$	(Ammoniacum)
Sagaresinotannol, $C_{24}H_{27}O_4(OH)$	(Sagapenum)
Dracoresinotannol, $C_8H_9O(OH)$	(Palm dragon's blood)

Panaxresinotannol, $C_{34}H_{49}O_7(OH)$	(Opopanax)
Xanthoresinotannol, $C_{43}H_{46}O_{10}$	(Yellow acaroid)
Erythroresinotannol, $C_{40}H_{40}O_{10}$	(Red acaroid)
Aloeresinotannol, $C_{22}H_{25}O_5(OH)$	(Aloes)
Asaresinotannol, $C_{24}H_{38}O_4(OH)$	(Asafetida)
Oporesinotannol, $C_{12}H_{13}O_2(OH)$	(Umb. opopanax)

Some of the resinotannols yield picric acid when treated with nitric acid; ammoresinotannol and sagaresinotannol yield trinitroresorcin; galbaresinotannol yields camphoric acid and camphoronic acid. When fused with potash, aliphatic acids are liberated and in some cases protocatechuic acid and resorcin.

2. Resin Acids

These acids all contain hydroxyl.

Abietic acid, $C_{20}H_{40}O_2$	(Colophony)
Pimaric acid, $C_{20}H_{30}O_2$	(Pine resin)
Succinoabietic acid, $C_{80}H_{120}O_5$	(Amber)
Sandaracolic acid, $C_{45}H_{66}O_7$	(Sandarach)
$C_{43}H_{61}O_3$ < OCH_3, OH, $COOH$	
Callitrolic acid, $C_{65}H_{84}O_8$	(Sandarach)
$C_{64}H_{82}O_5$ < OH, $COOH$	
Trachylolic acid, $C_{56}H_{88}O_8$	(Copal)
Isotrachylolic acid, $C_{56}H_{88}O_8$	(Copal)
Dammarolic acid, $C_{56}H_{80}O_8$	(Dammar)
Guaiacic acid, $C_{20}H_{26}O_4$	(Guaiacum)
Guaiaconic acid, $C_{19}H_{20}O_5$	(Guaiacum)
Copaibic acid, $C_{20}H_{30}O_2$	(Copaiba)
Elemic acid, $C_{35}H_{46}O_4$	(Elemi)
Masticinic acid, $C_{20}H_{32}O_2$	(Mastic)
Acid, $C_{13}H_{16}O_8$ Acid, $C_{26}H_{32}O_9$	(Myrrh)
Acid, $(C_9H_{13}O_2)_n$	(Bisabol myrrh)
Boswellic acid, $C_{32}H_{52}O_4$	(Olibanum)

3. Resenes

The classification of these substances is uncertain. They are indifferent to the usual class reagents and are insoluble in potash.

α-Panaxresene, $C_{32}H_{54}O_4$	(Opopanax)
β-Panaxresene, $C_{32}H_{52}O_5$	(Opopanax)
α-Dammarresene, $C_{33}H_{52}O_3$	(Dammar)
β-Dammarresene, $C_{31}H_{52}O$	(Dammar)

Fluavil, $C_{40}H_{64}O_4$	(Gutta percha)
Alban, $C_{40}H_{64}O_3$	(Gutta percha)
α-Copal resene, $C_{25}H_{38}O_4$	(Copal)
Dracoalban, $C_{20}H_{40}O_4$	(Palm dragon's blood)
Dracoresene, $C_{26}H_{44}O_2$	(Palm dragon's blood)
Masticin, $C_{20}H_{32}O$	(Mastic)
Resene, $C_{26}H_{34}O_5$	(Myrrh)
Resene, $(C_{29}H_{47}O_6)_n$	(Bisabol myrrh)
.Alibanoresene, $(C_{14}H_{22}O)_n$	(Olibanum)

METHODS FOR ANALYZING AND DETERMINING THE CONSTANTS OF RESINS

When working with resins of known identity the analyst can proceed to determine the constants by the methods described below which have been found most applicable. When the resin is of uncertain identity, or in case it is a new and hitherto unreported body, its general characteristics must be ascertained before proceeding with the estimation of its constants.

In order to arrive at a basis for future work the proximate analysis of the resin can best be obtained by following the procedure recommended by Tschirch.

The sample is dissolved in a suitable solvent, such as ether or chloroform, and shaken out successively with a 1 per cent solution of ammonium carbonate; a 1 per cent solution of sodium carbonate; a 0.1 per cent solution of potassium hydroxide; and a 1 per cent solution of potassium hydroxide. These reagents dissolve out the free resin acids, which can be recovered by acidulating with hydrochloric acid and shaking out with the proper solvent. The material remaining in the volatile solvent and which was inert to the alkaline solutions is distilled with steam, which removes any volatile substances and the solvent. The residue will consist of resin-esters and resenes. On saponification with alcoholic potash the acids liberated will go into the alkali, and on shaking up with ether the resin-alcohols and resenes are separated. The resin-alcohols are then separated from the resenes by acetylization or benzoyation. The identification of the acids may be accomplished by resorting to the regular scheme of qualitative organic analysis and with these data in hand and an approximate idea of the relative proportion of the resinous constituents, the proper methods of analysis can be selected.

Resin-esters predominate in benzoin, Peru and Tolu balsams, storax, acaroid resins, aloes resins and dragon's blood (all so-called benzo-resins) and in the umbelliferous gum resins, ammoniacum, galbanum, sagapenum, asafetida, and umbelliferous opopanax.

The resin acids predominate in the terpeno-resins from coniferous trees, colophony, copaiba, and Zanzibar copal.

The resenes predominate in the burseraceous oleoresins, myrrh, olibanum, bdellium, burseraceous opopanax, elemi, mastic, and the dipterocarpus products, Doona resin, dammar, and Manila copal.

When working with natural drugs an average sample may be prepared by grinding at least 100 grams of the dry drug as finely as possible. Balsams should be well shaken and resins containing water should be freed from moisture and stirred up well together. Gum resins which are soft and difficult to pulverize should be cooled by immersion of the mortar in a good refrigerant. When the parcel is large the samples should be drawn from various parts of the bulk.

A resin analysis may include the determination of the following data:

Acid Value. The number of milligrams of KOH combined by the free acid in 1 gram of resin during direct or back titration.

The acid value of the volatile portion is the number of milligrams of KOH combined by 500 mils of distillate obtained from 0.5 gram of gum resin by distillation with steam.

Ester Value. The difference between the saponification value and the acid value.

Saponification Value. (Hot—Cold). The number of milligrams of KOH combined by 1 gram of resin in hot or cold saponification.

The total saponification value (fractional sapon.) equals the number of milligrams of KOH combined by 1 gram of certain resins and gum resins on cold fractional saponification with alcoholic and aqueous alkali in succession.

Moisture.

Ash.

Amount Soluble in Alcohol.

Amount Insoluble in Alcohol.

Amount Soluble in Other Solvents.

Specific Gravity.

Resin Value. The number of milligrams of KOH combined by 1 gram of certain resins and gum resins on cold saponification with alcoholic alkali by itself.

Gum Value. The difference between the saponification value and the resin value.

Acetyl Value. The difference between the acetyl saponification value and the acetyl acid value.

Acetyl Acid Value.

Acetyl Saponification Value.

Acetyl Ester Value.

Carbonyl Value. The percentage of carbonyl oxygen in the substance taken.

Methoxyl Value. The amount of methoxyl furnished by 1 gram of resin.

Special determinations, such as cinnamein and resin esters in Peru balsam.

In the case of soft resins and balsams the weighing should be conducted on a watch-glass or a closed weighing bottle, removing the desired quantity by means of a glass rod, and inserting the rod and adhering material into the receptacle for conducting the assay.

In comminuting and reducing to a powder samples that are sticky, the end in view may be attained by storing the products in a cold place, which will usually render them hard and easily comminuted. Warming or heating in a drying oven should be avoided. All results should be calculated to the natural crude drug and not to goods dried at 100°.

(The methods herein offered have been correlated and tested out by Karl Dieterich, to whom full acknowledgment is accorded.)

Acid Value

1. Direct titration.
   (*a*) When the sample is soluble in alcohol, chloroform and suitable neutral organic solvent.
   One gram is dissolved in a suitable solvent or mixture and titrated with N/2 or N/10 alcoholic potash using phenolphthalein as indicator.
   (*b*) After the preparation of an alcoholic extract in the case of imperfectly soluble resins, the extract being used for titration. Applicable to gum resins, benzoin, storax.
   Same as above. The results may be calculated to 1 gram of the extract instead of the crude product.
   (*c*) Of the solution obtained by extracting a partially soluble resin with water and alcohol.
   Applicable to myrrh, bdellium, opopanax, and sagapenum. One gram of the finely ground resin is extracted by boiling with 30 mils of water under a reflux for fifteen minutes, followed by the addition of 50 mils of alcohol 96 per cent, and reboiling for an equal period. After cooling the extract is titrated without filtration with N/2 alcoholic potash.
2. Back titration.
   (*a*) In the case of completely (or nearly) soluble resins, free from esters, where the alkali combines with the acid and at the same time dissolves the resin.
   Applicable to dammar, sandarach, mastic, guaiacum, copal, etc.
   One gram of the finely divided (ester free) resin is left in con-

tact with 25 mils of N/2 alcoholic potash and 50 mils of petroleum ether in a stoppered flask for twenty-four hours or until solution has been carried as far as possible, and is then titrated back with N/2 sulphuric acid and phenolphthalein.

(*b*) In the case of partially soluble—esteriferous but sparingly saponifiable—resins, where the alkali fixes the acid and at the same time dissolves the resin.

Applicable to asafetida and olibanum.

One gram of the finely powdered substance is left for twenty-four hours in contact with 10 mils of N/2 alcoholic potash and 10 mils of N/2 aqueous potash in a stoppered flask. It is then mixed with 500 c.c. of water and titrated back.

(*c*) In the case of resins that are only partially soluble and contain esters, an aqueous alcoholic extract being employed.

Applicable to ammoniacum, galbanum, gamboge.

One gram of the finely divided resin is boiled for fifteen minutes under a reflux with 50 mils of water, after which 100 mils of strong alcohol are added and the whole boiled again for fifteen minutes. After cooling the whole is made up to 150 mils and filtered, 75 mils of the filtrate (equivalent to 0.5 of the sample) being treated for five minutes with 100 mils of N/2 alcoholic potash and then titrated back.

(*d*) In the case of soluble resins which contain esters and are easily saponified. The natural drugs are used. Applicable to benzoin.

Ten mils of N/2 alcoholic potash are allowed to act for five minutes on 1 gram of the drug, and then titrated back.

3. By estimating the volatile acids.

In the case of gum resins rich in ethereal oils.

Applicable to ammoniacum, galbanum.

0.5 gram of the sample is treated with a little water in a flask, and a current of steam is passed through, the flask being heated. The receiver contains 40 mils of N/2 aqueous potash, into which dips a tube from the condenser. Exactly 500 mils of distillate are collected, the condenser tube is washed out with distilled water and the whole titrated back. In this case the acid value gives the number of milligrams of KOH neutralized by 0.5 gram resin.

Ester Value

This is calculated by subtracting the acid value from the saponification value except in cases where the acid value has been determined as under 3,

and where a resin value and total saponification value are present. In such event the ester value cannot be calculated.

Saponification Value

1. By the hot method.
   (*a*) In the solutions of completely soluble resins.
   Applicable to nearly all balsams and resins for which no special methods have been devised.
   One gram of the resin is dissolved in 25 mils of N/2 alcoholic potash, boiled at temperature of steam-bath for one-half hour under a reflux, diluted with alcohol and titrated back.
   (*b*) In the case of previously prepared alcoholic extract of a partially or sparingly soluble resin.
   Applicable to gum resins, benzoin, storax.
   The same procedure as under *a*, except that an alcoholic solution of the extract is taken, the results being calculated to 1 gram of the crude drug and not of the extract.
   (*c*) In the case of gum resins partly soluble in water.
   Applicable to myrrh.
   The same procedure as under *a* except that the crude drug is taken after the addition of water to dissolve out the gum.
2. By the cold method.
   (*a*) In the case of perfectly soluble resins with cold alcoholic potash and petroleum ether only.
   Applicable to Peru balsam, copaiba, benzoin, storax.
   One gram of the substance is treated in a stoppered 500-mil flask with 50 mils petroleum ether (sp. gr. .700 at 15° C.) and 50 mils N/2 alcoholic potash. After standing twenty-four hours at room temperature, it is titrated back with N/2 sulphuric acid. In some cases (Peru balsam) it is necessary to add 300 mils of water to dissolve precipitated salts.
   (*b*) In the case of imperfectly soluble resins.
   This procedure is a fractional saponification, including "resin value" and "gum value," alcoholic and aqueous alkali, with an addition of petroleum ether, being used in succession.
   Applicable to ammoniacum, galbanum, gamboge, dragons blood, lactucarium.
   Two samples, each of 1 gram, of the resin are powdered and suffused in separate 1-liter stopper flasks with 50 mils of petroleum ether (sp. gr. 0.700 at 15° C.) followed by 25 mils of N/2 alcoholic potash. After standing closed for twenty-four hours at room temperature, with frequent shaking, the one sample is shaken up with 500 mils of water and titrated back with N/2

sulphuric acid; this gives the "*resin value.*" The second sample is then further treated with 25 mils of N/2 aqueous potash and 75 mils of water and left for another twenty-four hours with frequent shaking, being finally diluted with 500 mils of water and titrated back. This gives the "*total saponification value*" the difference between this and the resin value being the "gum value."

Acetyl Value

In the method proposed by K. Dieterich for determining the acetyl value of resins, the substance is boiled under a reflux condenser, with an excess of acetic anhydride and a little anhydrous sodium acetate, until completely dissolved, or until it is evident that no further portion will pass into solution. The solution is poured into water, and the precipitate then ensuing is collected and extracted with boiling water until perfectly free from all traces of uncombined acetic acid. The insoluble residues left by copal and dammar are also treated in the same manner. The dried acetylized products are then tested for the acetyl, acid, ester, and saponification values by dissolving 1 gram in cold alcohol and titrating with N/2 caustic potash. The saponification is also effected with N/2 alkali for half an hour under a reflux condenser, and the product titrated back after cooling down and dilution with alcohol (not water). As in the case of fats, the difference between the acetyl-saponification value and the acetyl-acid value gives the true "acetyl value."

Carbonyl Value

The substance under examination is warmed with sodium acetate and an accurately measured quantity of phenylhydrazine chloride in dilute alcoholic solution. The excess of hydrazine salt not sharing in the reaction is then ascertained by eliminating the nitrogen by oxidation with Fehling's solution and collecting the gas in a measuring tube. The carbonyl value, i. e., the percentage of carbonyl oxygen in the substance taken, is ascertained by the formula $O = V - Vo \frac{0.07173}{S}$, wherein $V - Vo$ indicates the difference in the volume of nitrogen reduced to O or 760 mm., and S refers to the weight of the substance in grams.

Methoxyl value (Zeisel)

As this method entails the use of apparatus and special precautions, it is considered preferable to repeat the author's own description in full.

The Zeisel apparatus is made up as follows: A reflux condenser, fed

with water at 40–50° C., is fitted with a small flask, the neck of which is provided with a lateral tube for the introduction of carbon dioxide. The upper end of the condenser tube is connected with a Geissler potash apparatus which is charged with amorphous phosphorus suspended in water, and is placed in a water-bath kept at about 50–60° C., its purpose being to free the current of alkyl-iodide vapor passing through from hydriodic acid and iodine vapor. The alkyl iodide is led into a 4 per cent solution of silver nitrate in two successive flasks, the whole being generally retained and converted into silver iodide in the first one. In performing the experiment, the substance to be examined for methoxyl is heated along with 10 c.c. of hydriodic acid of sp.gr. 1.68, CO_2 being passed through the apparatus. The experiment is complete when the liquid in the first flask has become clear above the deposit of silver iodide, and the silver iodide is then determined by gravimetric means.

For ordinary analyses it is sufficient to use 50 mils of the silver nitrate solution in the first flask, and 25 mils in the second, after acidification with a few drops of nitric acid free from nitrous acid. After the reaction is terminated—Zeisel's conditions being otherwise maintained throughout—the clear liquid above the silver iodide is poured off into a 250-mil measuring flask. The silver nitrate solution in the second flask is diluted with water and poured into the same measuring flask, the contents of which are thereupon made up to the mark with water, agitated well, and passed through a folded filter into a dry vessel.

For the titration, 50 or 100 mils of the filtrate are used, after suitable acidification with nitric acid (free from nitrous acid) and an addition of ferric sulphate solution.

SEPARATION OF RESIN ACIDS AND FATTY ACIDS

In the case of a fatty acid adulterated with resin, about 0.6 gram of the substance is dissolved in 20 mils of 95 per cent alcohol. To this solution is added a trace of phenolphthalein, and a solution of alcoholic potash is run in, drop by drop, from a burette, with continued stirring, until the indicator has assumed a dark red color, characteristic of alkalinity.

After adding one or two drops of the potash solution in excess, the flask containing the liquid is placed on the water-bath and the contents boiled for ten minutes. When cold, the whole is poured into a 100-mil test-tube, the flask washed with ether, and—the whole being made up to 100 mils with this solvent—the tube is corked and shaken up thoroughly.

Next, 1 gram of finely divided silver nitrate is introduced and shaken up well for ten to fifteen minutes, until the flocculent deposit of silver stearate or oleate has collected together at the bottom of the tube. Then 50–70 mils of the clear liquid are removed by means of a pipette, and

transferred to another 100-mil test-tube, where a further small quantity of silver nitrate is added to remove the fatty acid still in solution. The clear liquid is then mixed with 20 mils of dilute hydrochloric acid (one-third 21 per cent HCl and two-thirds water); an aliquot part of the supernatant ethereal solution is evaporated in a platinum basin, the residue—dried in the steamer—being resin, accompanied by a little oleic acid. Direct experiment has shown that, under these conditions, 10 mils of ether retain on an average 0.00235 gram of oleic acid, so that the result of the analysis may be corrected by means of this coefficient. The method is applicable to the determination of resin in linseed oil, soap, etc.

CLASSIFICATION OF INDIVIDUAL RESINOUS SUBSTANCES

Resins	*Oleo Resins*	*Balsams*	*Gum Resins*
Aloes	Canada Balsam	Peru	Ammoniacum
Anime	Copaiba	Tolu	Bdellium
Amber	Cubeb		Euphorbium
Benzoin	Gurjun Balsam		Galbanum
Colophony			Gamboge
Dragon's Blood			Lactucarium
Elemi			Myrrh
Guaiacum			Sagapenum
Jalap			Asafetida
Kino. Red Gum			Olibanum
Labdanum			Opopanax
Mastic			
Sandarach			
Scammony			Chicle
Shellac			Gutta Percha
Storax			Caoutchouc
Tacamahac			
Thapsia			
Turpentine			
Turpethum			
Podophyllum			

Of these Benzoin, Storax, Peru, and Tolu Balsams are treated more conveniently in the discussion of aromatic acids. Jalap and Scammony have been treated, and Podophyllum and Cubeb have also been described.

Of the remainder the most important from the point of view of medical usage are Guaiacum, Kino, Turpentine, Copaiba, Ammoniacum, Gamboge, Lactucarium, Myrrh, and Asafetida. The others have but a limited use as therapeutic agents or are employed only for their mechanical effect in the preparation of plasters, varnishes, and coverings for wounds and abraded surfaces and for coloring mouth washes.

GUAIACUM RESIN

Guaiacum resin is obtained from the wood of Guaiacum officinale and G. sanctum (Zygophyllaceæ). These trees grow in Cuba and some of the other West India Islands, the Bahamas, Hayti, and Jamaica. The wood is used medicinally for the same purposes as the resin. It is a hard, heavy wood, and known commercially as *lignum vitæ*.

The resin occurs in irregular or somewhat globular masses of a glassy luster and resinous fracture. The color is deep greenish brown or dark olive on the outer surface; the internal color which has not been exposed to the air is reddish brown or hyacinth, diversified with shades of various colors. It is brittle and presents a shining, glassy surface when broken. The taste is not perceptible at once, but soon becomes acrid and leaves a permanent sensation of heat and pungency.

Guaiacum is employed as an alterative, stimulant, diaphoretic, and anti-rheumatic. It is dispensed in the form of a plain tincture and with aromatic spirit of ammonia. Liquid sarsaparilla compound contains guaiacum with sarsaparilla, sassafras, licorice, and mezereon bark. Compound tincture of guaiac or Dewer's tincture contains guaiac, potassium carbonate, and pimento, and is a remedy for suppressed menstruation.

Some of the pill and tablet formulas which may be mentioned include the N. F. Antimony Comp. (Plummer pills) which contains guaiac, calomel, sulphurated antimony, and castor oil, it will also be found combined with copaiba, cubeb, and ferric citrate; with calomel and opium; with aloes, sulphur, Podophyllum, and frangula; with potassium iodide, Phytolacca, colchicin, and digitalin (anti-rheumatic); with salicylic acid, sodium bicarbonate, and Colchicum; with cantharides, aloes, and ferrous sulphate (emmenagogue); with ammonium chloride, licorice, and Hydrastis (throat); with senega, squill, aconite, Grindelia, ammonium carbonate, and ammonium bromide; with terpin hydrate, opium, wild cherry, and belladonna. It is dispensed alone in lozenges and may be found combined with Sanguinaria.

Guaiacum mixture is an emulsion of guaiac with tragacanth, sugar, and cinnamon water.

Guaiac occurs as the crude resin in which condition it is mixed with fragments of wood and bark and dirt; as the purified resin and in the form of tears. The pure resin consists of guaiacum resin ($C_{20}H_{23}O_3OH$); guaiaconic acid ($C_{20}H_{22}O_3(OH)_2$); guaiacic acid ($C_{21}H_{19}O_4(OH)_3$); guaiacol and guaiacum yellow ($C_{20}H_{20}O_7$). It often contains up to 9 per cent of gum.

Pure resin is almost completely soluble in alcohol, chloroform, and acetic ether, and all but about 10 per cent is soluble in ether and benzol, though Evans reports commercial samples running as high as 11.7 per cent.

Pure resin has only a slight amount of ash. The acid value may run from 89–98, but Dieterich records the tears as running from 72–76, and Evans finds 45–56. The methoxyl values have been reported from 73.8–84.

Dieterich has determined the acetyl values and found

Acetyl

	Acid Value	Ester Value	Sapon. Value
Purified	13.57–14.89	149.33–149.75	163.22–164.22
Commercial Crude	45.84–53.15	121.75–129.16	167.59–192.44

Dieterich recommends the following procedure for determining the acid value. One gram of the resin is suffused with 10 mils N/2 alcoholic potash and 10 mils N/2 aqueous potassium hydroxide, and left for twenty-four hours in a glass-stoppered flask. After adding 500 mils of water the liquid is titrated back with N/2 sulphuric acid and phenolphthalein.

Adulteration with colophony is indicated by a high acid value and the adulterant can be identified by the Storch-Morawski test applied to the abietic acid, which is first separated by treating an alcoholic solution with an excess of potassium hydroxide.

Guaiac is adulterated with a similar product of yellowish-brown color known as Peruvian guaiacum (Guaiacum peruvianum odoriferum). Admixture with this resin may be detected, according to Hirschsohn, by treating a chloroformic solution with bromin fumes, which produce a red color, whereas pure guaiac solutions turn blue.

An alcoholic solution of guaiac gives a blue color with tincture of ferric chloride, manganic and silver salts, nitric acid, chlorin, gluten, mucilage of acacia, milk, and with hydrocyanic acid, followed by copper sulphate. Citric acid prevents the production of the color with ferric salts, and egg albumen reduces the sensitiveness. It dissolves in cold concentrated sulphuric acid to a rich claret-colored solution which on dilution deposits a lilac-colored precipitate. Mammalian blood-stains, moistened with the tincture and followed by a few drops of dilute hydrogen peroxide, become blue in color.

When analyzing a medicine guaiac will remain undissolved when an evaporated alcoholic extract of the product is treated with water. On treating the residue with chloroform, the guaiac will dissolve and the solution may be filtered from any insoluble material, evaporated, and the residue dissolved in alcohol. Strips of clean white filter paper should be moistened with this tincture and when nearly dry exposed individually to the fumes of nitric acid and chlorin, which should produce blue colors in the presence of guaiac. Other strips should be moistened with tincture of ferric chloride and with hydrocyanic acid and copper sulphate. Drops of the tincture should be added to gluten, mucilage of acacia, and milk,

all of which should give positive reactions. A test should be obtained with blood-stains using the tincture followed by hydrogen peroxide.

In the absence of other resinous drugs the proportion of guaiac in a medicine can be determined by extracting the powdered substance with alcohol, or treating an evaporated liquid mixture with alcohol. In either case the alcoholic extract thus obtained should be concentrated and poured into an excess of water, which will precipitate the resin. The liquid is decanted through a filter and after washing with water the resin is dissolved in chloroform and the chloroformic liquid shaken with dilute sulphuric acid. If the acid removes any basic substances the shaking is continued with successive portions of acid until a test with Mayer's reagent produces no precipitate. The chloroform is then washed with water, filtered into a tared dish, evaporated and the residue weighed.

KINO

The resins and gum-resins known as "Kinos" are obtained from a number of different sources. The resin which is known to the pharmacist as kino is obtained from Pterocarpus marsupium (Papilionaceæ). Kinos from Eucalyptus rostrata and other species of Eucalyptus are known as "red gum."

Kino is employed as an astringent. It is dispensed as a tincture and in pills and tablets, combined with camphor, opium, and Capsicum; diarrhea tablets contain kino, opium, camphor, bismuth subnitrate, sodium bicarbonate, and mercury with chalk.

Red gum is a component of astringent lozenges and mouth washes, and is also used in seasickness.

Kinos consist of dark-red or reddish-black resinous appearing brittle masses or granules, having an astringent taste and imparting a red color to the saliva. They dissolve in part or swell up in the presence of water, and the Pterocarpus kino is soluble in alcohol. They also dissolve in alkalies, but are nearly insoluble in ether.

The resin of Pterocarpus marsupium contains a large porportion of a tannin known as kino-tannic acid, ash, kino-red, pyrocatechuic acid, and woody trash. The alcoholic solution tends to gelatinize. Aqueous solutions give a green color with ferric sulphate, changing to violet on the addition of alkali carbonates or acetates. Ferric chloride produces a green precipitate which turns purplish red in the presence of alkalies. Dilute mineral acids throw out a flocculent precipitate. The aqueous solution is precipitated by gelatin, and the soluble salts of silver, lead, mercury, and antimony.

Commercial kinos differ in their properties. Good kino should show from 90–98 per cent soluble in 90 per cent alcohol, 85–95 per cent soluble

in water, 50–60 per cent tannin, not over 3 per cent ash and from 8–18 per cent moisture. The U. S. P. is considerably less rigid in its solubility requirements and provides for a product which should yield not less than 45 per cent to alcohol and not less than 40 per cent to boiling water.

Eucalyptus kino is claimed to contain gallic acid and catechin in addition to the other constituents reported in Pterocarpus. Thum found that less than 20 per cent was soluble in boiling water and that a solution of any strength would gelatinize unless glycerin was present

THAPSIA RESIN

Thapsia resin is obtained from Thapsia garganica (Umbelliferæ). It is a strong counterirritant and is sometimes used in plasters. The resin and the root of the plant when handled cause intense itching of the hands and exposed membranes.

The blistering substance crystallizes and is reported to have a melting-point of 87° C. By successive extraction with alcohol and ether two resins have been separated, the former giving a scarlet color with sulphuric acid and the latter a blue color.

Dieterich has developed a procedure for examining thapsia resin which avoids the dangerous consequences which would result by operating under ordinary conditions.

About 1 gram of Thapsia resin is mixed with a sufficient amount of pure sand, and the crumbled mass placed in a Schleicher & Schull cartridge, the weight of cartridge+sand+resin being noted, as well as that of the cartridge+sand, and of the resin by itself. The whole is then treated, in a Soxhlet extractor, with petroleum ether for three hours, and, after cooling down, the cartridge is dried in the oven at 80° C. until no further odor of petroleum ether is discernible; longer drying must be avoided in view of the moisture-content of the resin. The cold petroleum ether extract is next treated with 20 mils of alcoholic N/2 caustic potash and boiled for half an hour under a reflux condenser, the apparatus being tightly stoppered. After cooling, the saponification value of the portion soluble in petroleum ether is determined by the usual method and the results are referred to 1 gram.

The percentage soluble in petroleum ether is found, indirectly, by calculation, from the loss in weight of the aforesaid cartridge, and expressed as a percentage. The cartridge is then replaced in the extractor, and, after charging the bottom flask with 20 mils of alcoholic N/2 caustic potash and 50 mils of alcohol, is extracted for two hours longer. The alcohol serves as the extracting reagent, while the underlying alkali immediately saponifies the dissolved substances. After two hours the whole apparatus is cooled, and the cartridge is then dried at 100° C. until constant.

The extra loss in weight, calculated in percentages, gives the value of the portion soluble in alcohol; the residue, which is easily calculated by deducting the weight of cartridge+sand from the total weight of cartridge+sand+resin, expresses the value, insoluble residue.

The saponification liquid in the flask is titrated and—calculated to 1 gram—gives the saponification value (hot) of the portion soluble in alcohol.

The total saponification value (hot) of the original resin is found by saponifying 1 gram of the resin with 25 mils of alcoholic N/2 potash, under a reflux condenser, and titrating back when cold.

The following data were obtained on authentic thapsia:

	Per Cent
Moisture	7.43– 10.33
Ash	0.16– 0.415
Soluble in petroleum ether	19.28– 25.67
Soluble in alcohol	83.46– 89.32
Total Saponification value	336.33–384.47

Thapsia is adulterated with euphorbium and the resins of Thapsia villosa, which contains acrid substances but is milder in its action.

TURPENTINE

The various species of Pinus (the pines), Picea (the spruces), Abies (the firs), Tsuga (the hemlocks), and Larix (the larches), of the Pinaceæ yield oleoresinous exudations to which the name turpentine is given.

The pines which furnish the greater part of the turpentine gathered in the United States are P. palustris, the long-leaved or Georgia pine; P. tæda, the loblolly or old field pine; P. echinata, the yellow or spruce pine, and P. heterophylla, the Cuban or swamp pine.

The exudation from Abies balsamea, the balsam fir, is known as Canada balsam, but the balsams from A. fraseri and Tsuga canadensis, the hemlock, are collected for this product. A. excelsa yields Burgundy pitch.

Venice turpentine is an exudation from the European Larix decidua.

Russian turpentine is obtained from Pinus sylvestris, the type species of the Pinus, and which is regarded by some authors as belonging to a distinct genus from the several species of Pinus indigenous to the United States.

Chian turpentine is obtained from Pistacia terebinthus and Strasburg turpentine from Abies picea.

Turpentine consists of a complex mixture of turpentine oil, resin acids, colophony, and other substances. Turpentine oil, the limpid volatile fraction of the oleoresin, consists largely of *d*-pinene. Exception to this general statement occurs in the case of the French oil from P. pinaster (P. maritima). Camphene also occurs in turpentine oil.

Turpentine or more often the oil of turpentine is used externally as a rubefacient and counter-irritant and will be found with various other substances in liniments and embrocations. Internally it is employed as an anthelmintic, stimulant, hemostatic, emmenagogue, and antiseptic.

It will be found in emmenagogue pills, in gonorrhea mixtures, cough tablets and elixirs and combined with copaiba and oil of cubeb in gelatin capsules. It is employed in remedies for dropsy as a diuretic, for tape worm, for rheumatism, and as an antidote for phosphorus poisoning.

In many cases Venice turpentine will be found functionating in place of the Pinus turpentine.

Chian turpentine has been employed in the treatment of cancer.

The turpentines are liquid when freshly gathered, but soon become thick on exposure, due to loss of volatile oil and oxidation. They soften on heating and burn with a smoky flame. They dissolve in the ordinary volatile solvents and in the fixed and volatile oils. When taken internally or applied to the skin they impart a violet odor to the urine.

The acid value of turpentine ranges from 100–145. The ester value is reported from 2–60, the saponification value 108–180. Venice turpentine has a lower acid value, 60–80, and saponification values as low as 81 are reported, refractive index 1.518–1.521. Kremers reports the following rotation figures:

$(\alpha)_D$ oleoresin P. palustris..... $-13.665°$
$(\alpha)_D$ oil P. palustris..... $+23.93°$
$(\alpha)_D$ oleoresin P. cubensis..... $-32.428°$
$(\alpha)_D$ oil P. cubensis..... $+ 9.6°$

Dieterich reports the following acetyl value for ordinary turpentine:

Acetyl:

Acid value 123.75–125.55
Ester value 62.32–93.79
Saponification value 187.87–217.04

For Venice turpentine:

Acetyl:

Acid value 69.87–72.19
Ester value 109.08–118.67
Saponification value 178.95–190.86

The admixtures of ordinary turpentine with Venice turpentine may be recognized by a consideration of the acid, saponification, and acetyl values.

Pinus turpentine when added in small quantity to strong ammonia water produces a milky mixture which will set to a jelly when the proportion is about 1–5. Venice turpentine, under similar conditions, does not

distribute itself; the liquid remains clear, and subsequently the turpentine is converted into a semi-solid, colorless, opaque mass.

Pinus turpentine sets into a hard mass when mixed with 20 per cent of its weight of calcium hydroxide. Venice turpentine does not set immediately when mixed with this reagent.

Haarlem Oil

This product formerly enjoyed an enormous sale in the United States. It is an old remedy and the genuine Haarlem oil gets its name from the town in which it was first manufactured in Holland. Several formulas, more or less similar, have appeared in the market, all bearing the name Haarlem oil. The original claims for this mixture were about the most far-reaching of any claims that have been attached to any remedy in modern times, and after reading them the patient might believe himself to be the possessor of the panacea of all evil and the golden touch of old King Midas. The principal ingredients were linseed oil, which had been boiled with sulphur, and turpentine.

Chian Turpentine

The specific gravity is reported 1.050 but varies with the percentage of volatile oil. It is readily and almost completely soluble in the ordinary volatile solvents and according to E. Dieterich has acid value *d.* 47.13–48.53; ester value 19.13–21.47; saponification value, *h.* 66.26–70.00.

Abietic Acid, $C_{20}H_{40}O_2$

Abietic or sylvic acid is the chief constituent of colophony or common rosin, though it has been reported that some samples of authentic identity contained none. Colophony is the anhydrous residue left on the distillation of the turpentine obtained from different trees of the Pinus family. When pure, abietic acid is a white crystalline substance melting 182°, (156–162° Cohn), insoluble in water but dissolving in alcohol, ether, benzol, and glacial acetic acid. When treated with strong ammonia it is converted into a gelatinous mass which dries to a solid resin, readily soluble in water. Copper abietiate is soluble in ether.

In analytical work abietic acid is seldom obtained pure, but in admixture with the other rosin acids. They are easily removed from ethereal solution by shaking with caustic alkali and then removed from the alkaline liquid by adding excess of acid and shaking out with ether. The ether on evaporation leaves a residue of free acid which can be separated from phenols or any moderately soluble acids if these are present, by washing with boiling hot water. The rosin acids after the above treatment can be subjected to the Liebermann-Storch (Storch-Morawski)

reaction. A portion of the residue is dissolved in warm acetic anhydride and after cooling, sulphuric acid (1–1 by volume) is allowed to flow into the solution, producing a reddish-violet color.

Kauri resin gives a deep violet-red color changing to brown; amber and East India and black dammar resins, deep wine red changing to brown; Manila, pontianac, and Borneo resins, dark brown, Batavia, and Singapore dammar resins, deep wine red which does not change on standing. Some specimens of Manila give a reaction similar to that of abietic acid.

The copper acetate test for abietic acid is obtained by dissolving the resin in alcohol, transferring to a separatory funnel and adding an equal volume of petroleum ether. When mixed by agitation, water is added and the whole shaken for thirty seconds. After separating, the aqueous layer is drawn off and the petroleum ether washed with water until both layers are clear. Thirty mils of a $\frac{1}{2}$ per cent solution of copper acetate are added, shaken and the appearance of a green color in the petroleum ether indicates abietic acid.

Rosin is used as the adhesive agent in certain forms of plaster and the general directions for handling this class of products qualitatively is given in detail in my work on Qualitative Analysis.

One well-known plaster in general use consists of rosin and tartar emetic. If it is desired to determine the latter ingredient, the plaster or a known proportion of it is treated with absolute ether, which dissolves the resin and leaves the tartar emetic behind. The ether solution is filtered off and the container and filter washed with ether, until free of rosin. The tartar emetic is then dissolved in water and the antimony precipitated by hydrogen sulphide and the determination finished as detailed under Antimony.

CANADA BALSAM

Canada balsam is a clear, pale yellow (almost greenish) and slightly fluorescent viscid liquid, with a pleasing odor and bitter taste, and solidifying on exposure to the air. It is completely soluble in chloroform, benzol, and acetic ether, largely soluble in ether and oil of turpentine and partly soluble in alcohol and petroleum ether. It solidifies when mixed with magnesia and water. Its acid value is reported from 81.3–86.8; ester value 4.54–13.1; and saponification value, hot 89.43–95.76; refractive index 20°, 1.5194–1.523.

Dieterich, quoting Bonastre, gives the composition of Canada balsam as follows:

	Per Cent
Lævorotatory ethereal oil	18.6
Resin soluble in alcohol	40.0
Resin sparingly soluble in alcohol	33.4
Caoutchouc	4.0
Bitter principles, extractives, trace of acetic acid	4.0

Tschirch, working on more modern lines, has isolated resinol acids standing in a certain relationship to abietic and pimaric acids.

Canada balsam is used in chronic bronchitis and as a stimulant to the mucous surfaces in catarrhal affections. It will be found in some of the prescription remedies recommended for diseases of the throat and lungs. Mixed with collodion it produces a very effective skin varnish.

MECCA BALSAM

Mecca balsam or balm of Gilead is a terebinthinate-like exudation from Balsamodendron gileadense syn. Commiphora opabalsamum, Bursuraceæ, and has been employed in medicine for the same purposes generally as Canada balsam and the turpentines. It contains about 10 per cent of volatile oil and is soluble completely in ether. It is not completely dissolved by alcohol and petroleum ether. The data regarding the action of other volatile solvents are discrepant, but this is probably due to the condition of the samples reported on.

Dieterich examined fresh and old resinified meccas and obtained the following data:

	Fresh	*Old*
Acid value	39.84– 39.96	60.77–61.37
Ester value	101.1 –101.39	81.90–82.66
Sapon. value, cold	140.94–141.35	142.67–144.03

He observed that when fresh the balsam had a very pale color, highly agreeable aromatic odor, and lower specific gravity than the old, the latter having a turpentine-like odor and was dark brown and viscid.

COPAIBA BALSAM

Several species of Copaiba and Hardwickia (Leguminoseæ) yield oleo-resinous exudations extensively used in diseases of the mucous membrane of the genito-urinary organs and in chronic skin diseases such as leprosy and psoriasis. The medicinal copaiba is limited officially to the genus Copaiba and the commercial oleo-resins are obtained from South America, the Brazilian tree, C. langsdorfii being one of the chief sources. C. copallifera of West Africa exudes an oleo-resin closely resembling the South American product, and Hardwickia manii of Africa and H. pimenta of India also furnish drugs which to all intents and purposes answer the description of copaiba balsam.

Gurjun balsam, which resembles copaiba, and is often mixed with it, possesses medicinal properties similar to those of copaiba. It comes from several species of Dipterocarpus (Dipterocarpaceæ) growing in the East Indies.

Copaiba is administered in capsules, pills, and tablets; it is combined principally with oleoresin cubeb, santal wood oil, olive oil, and methylene blue. Other medicinal agents sometimes added to the ordinary copaiba mixtures include turpentine, buchu, matico, Krameria, salol, pepsin, guaiac, ferric citrate, iron and ammonium citrate, and ferrous sulphate. Copaiba resin deprived of its volatile oil is occasionally used medicinally.

There are several varieties of copaiba distinguished by names representative of the countries of their production or the ports of shipment. The chief commercial varieties are the Maracaibo, Maranham, and Para. The former are representative of the type of thick balsams and the latter of the thin.

Copaiba consists of from 40–75 per cent of volatile oil and 60–25 per cent of resin. Caryophyllene has been detected in the volatile oil. The peculiar and almost characteristic odor of copaiba is due to the volatile oil, and this odor is generally observed in the breath of a patient to whom the drug has been administered.

Copaiba balsam consists of amorphous resin acids, resenes, crystalline resin acids, and volatile oil. The volatile oil will run from 40–75 per cent. The crystalline resin acids have been studied. Para balsam contains paracopaivic acid, $C_{20}H_{32}O_3$, melting 145–148°, soluble in ammonium carbonate solution; and homo-para-copaivic acid, $C_{18}H_{28}O_3$, melting 111–112° and insoluble in ammonium carbonate. Maracaibo balsam contains metacopaivic acid, $C_{11}H_{16}O_2$ or $C_{16}H_{24}O_3$, melting 89–90° C. Illurinic acid has been reported in Maracaibo balsam. It is one of the constituents also of African copaiba.

Bitter principles are present in all varieties. The analysis of copaiba has been handicapped because of the uncertainty of the purity of the product under examination and many of the published reports are therefore unreliable. Adulteration has been practiced with gurjun balsam, olive and castor oils, storax, colophony, turpentine, sassafras oil, paraffin, etc., and often one variety of copaiba is mixed with another.

The U. S. Pharmacopœia specifies that the official oleoresin shall contain not less than 36 per cent resin, and shall have an acid value of not less than 28 nor more than 95. It should be soluble in an equal volume of petroleum ether, a further addition of the solvent producing a flocculent precipitate. The volatile oil distilled from copaiba should not boil below 250° and should have a rotation not less than −70 at 25° C. in a 100-mm. tube.

The specific gravity of copaiba runs from .95–.97 in the case of Para and .98–.99 in the case of Maracaibo, though old samples of the latter will run slightly over 1. Maracaibo oleoresin is completely soluble in ether, chloroform, petroleum ether, oil of turpentine, and carbon disulphide, and almost completely in 90 per cent alcohol and acetic ether. Para copaiba

is not as completely soluble in petroleum ether and carbon bisulphide as the Maracaibo, but otherwise shows the same solubility.

The examination of a sample of copaiba should include the determination of the constants and reactions prescribed in the Pharmacopœia, and in addition the saponification and ester values. In order to test the volatile oil, a complete separation of this ingredient should be effected by steam distillation, and the separated oil filtered. It would be useless to attempt to determine the boiling-point of the oil by distilling it from the oleoresin directly over a flame.

In order to determine the acid, saponification, and ester values, the procedure recommended by Dieterich will prove advantageous.

Acid value, direct, 1 gram of the oleoresin is dissolved in 200 mils of 96 per cent alcohol and titrated with N/2 alcoholic potash in presence of phenolphthalein. The volume of alkali consumed multiplied by 28.08 gives the acid value.

Saponification value, cold. One gram is placed in a stoppered 1-liter flask and treated with 20 mils N/2 alcoholic potash and 50 mils petroleum ether (sp. gr. 0.700). After standing for twenty-four hours at room temperature, the contents are diluted with 95 per cent alcohol and titrated back with N/2 sulphuric acid and phenolphthalein. The saponification value is found by multiplying the volume (mils) of combined KOH by 28.08.

The ester value is found by calculation.

The results of the examination of a number of samples of authentic copaibas are tabulated below:

K. Dieterich has reported an interesting research where he added known amounts of the well-known adulterants to authentic Maracaibo and Para oleoresins and determined the specific gravity, acid, saponification, and ester values. He concludes that the added adulterants modify the constants of the normal Maracaibo copaiba in the following manner:

1. Gurjun balsam increases specific gravity, lowers acid value, and raises saponification and ester values.

2. Olive oil reduces specific gravity and acid value, but considerably increases the ester and saponification values.

3. Sassafras oil heightens specific gravity, lowers acid and saponification values, leaving ester value almost unchanged.

4. Oil of turpentine reduces specific gravity, acid value, and saponification value, but considerably increases ester value.

5. Venice turpentine increases specific gravity, acid and saponification values, leaving ester value almost unchanged.

6. Colophony greatly increases specific gravity and acid value. No definite conclusions deducible from ester and saponification values.

Variety	Sp. Gr.	Acid Value	Saponification Value (cold)	Ester Value	Refractive Index 15° C.	Investigator
Maracaibo	.980–.990	75.0–85.0	80–90	3.0–6.0		K. Dieterich
Maracaibo old	1.001	93.88–94.33	97.56–101.35	3.68–7.02		K. Dieterich
Maracaibo		79.1–91.4			1.5076–1.519	Evans
Para	.95–.97	40.0–60.0	30.0–60.0	2.0–8.0		K. Dieterich
Para		49.47–61.86	64.62–70.75	9.06–18.06		K. Dieterich
Para		29.4–65.80	31.30–67.70	1.90		E. Dieterich
Para		21–72.1			1.4992–1.5132	Evans
Maranham		63–89.6			1.5098–1.5164	Evans
Angostura	.980–1.009 (Prael)	75.87–83.5	91.44–98.08	7.94–17.38		K. Dieterich
Bahia	.980 (Prael)	81.09–81.27	86.17–87.32	5.08–6.08		K. Dieterich
Carthagena	.958 (Prael)	87.75–88.23	92.3–92.9	4.55–4.67		K. Dieterich
Maturin	.983 (Prael)	72.52–82.73	91.38–92.02	9.29–12.86		K. Dieterich
Surinam	.942		34 (hot)			Pool
West African (Hardwickia manii)	.990	57.60				Gehe
West African		58.74–59.33	68.36–68.95	9.62		K. Dieterich

7. Liquid paraffin reduces specific gravity and acid value, increases ester value, but leaves saponification value about normal.

8. Castor oil reduces specific gravity and acid value. considerably increasing ester and saponification values, like olive oil.

9. Resinified old balsam. The acid and saponification values and specific gravity are greatly increased, analogous to the influence of colophony.

The effects of adulterants on normal Para balsam may be stated as follows:

1. Gurjun balsam increases the specific gravity, saponification and ester values, and reduces acid values.

2. Olive, castor, and other fatty oils lower the specific gravity and acid value, but considerably increase the saponification and ester values.

3. Sassafras oil heightens the specific gravity, but depresses the acid and saponification values.

4. Oil of turpentine lowers the specific gravity and acid value, but largely increases the ester value.

5. Venice turpentine raises the specific gravity, acid, saponification, and ester values.

6. Colophony raises the specific gravity, acid and saponification values.

7. Liquid paraffin reduces the specific gravity, greatly lowers the acid value, and increases the ester value.

Many color tests have been proposed for the detection of adulterants, but practically all have been discarded as unreliable. The U. S. Pharmacopœia recognizes one reaction for the presence of Gurjun balsam to be applied on the volatile oil, 3–4 drops of the oil distilled from the balsam with steam are treated with 3 mils of glacial acetic acid and 1 drop of freshly prepared sodium nitrite solution (1–10) and underlaid with 2 mils of concentrated sulphuric acid. The acetic layer should not show a pink color.

Deussen [1] claims that the optical rotation of the oil furnishes the most important information. The balsam is distilled with steam as completely as possible; the oil is separated from the distillate, dried with sodium sulphate, filtered and the rotation determined.

Oil of Copaiba (Maracaibo or Para)

The oil distilled from copaiba oleoresin is a colorless, yellowish, or brownish liquid, with the characteristic odor of the drug, and a bitter, grating taste. It has a specific gravity 0.900–0.910; $(\alpha)_D = -7$ to 35°; boiling 250–275°; refractive index 1.4943–1.5026 (Evans).

[1] Arch. Pharm., 242, 1914, 590.

It is not completely soluble in 90 per cent alcohol, but dissolves in an equal volume of absolute alcohol.

Deussen states that the specific rotatory power of an oil from an unadulterated Maracaibo oleoresin calculated for a 10 cm. tube should be between -2.5–$14°$.

The oil from Maranham balsam has sp. gr. 0.889–0.90; rotation = $-13°$ to $-21°$; refractive index 1.494–1.4992 (Evans).

The sesquiterpene caryophyllene, $C_{15}H_{24}$, has been isolated from the oil and may be separated from the fraction distilling between 250–270° by treatment with glacial acetic acid and sulphuric acid and warming on the water-bath, which throws out the hydrate, $C_{15}H_{25}OH$, melting 94–96° C. The hydrate may be freed from the oily material by filtering and then crystallized from alcohol.

A volatile oil has been reported from an African copaiba. This product had specific gravity .917–.918· rotation = $+20° 42'$. No caryophyllene was obtained.

AFRICAN OR ILLURIN COPAIBA

This balsam contains from 2–3 per cent of illurinic acid, $C_{20}H_{28}O_3$, melting 128–129° C. This acid is crystalline and strongly lævorotatory $(\alpha)_D = -54° 89'$. The crystalline barium salt is characteristic and may be obtained when an ethereal solution of the acid is shaken with barium hydroxide solution. A few needles appear in a short time and then suddenly the whole ether layer is covered with a network of fine needles.

The volatile oil from African copaiba rotates the plane of polarized light to the right, thus differing radically from the oils of South American copaiba, which are lævogyrate.

According to the present rulings, the substitution of African copaiba for the official varieties constitutes an adulteration.

GURJUN BALSAM

Gurjun balsam has a specific gravity of .955–.979, acid value 5.0–10.98 saponification value 10–26.35, and ester value 1–15.37; most of these values being determined by K. Dieterich. By steam distillation up to 70 per cent of oil are obtained. The odor and taste resemble copaiba. The color is greenish gray; with reflected light somewhat turbid and slightly fluorescent, with transmitted light, clear and reddish brown.

The volatile oil is a yellow, somewhat viscous liquid, sp. gr. .915–.930; $(\alpha)_D = -35°$ to $130°$. It distills almost completely between 225°–256°. It is not completely soluble in 90 per cent alcohol. Its chief constituent is a sesquiterpene, $C_{15}H_{24}$, but its identity has not been determined.

It is claimed that when taken internally, gurjun balsam imparts no unpleasant odor to the breath.

The chief concern of the analyst is in the testing of the commercial drug and with the data and directions set forth the examination should present no difficulties.

The presence of copaiba in a medicine is usually apparent by the odor, though if the resin alone has been used the odor may be faint or even absent. The question then may be to determine whether the oleoresin or the volatile oil has been used or whether copaiba or gurjun is the medicament in hand. Being a complex mixture itself, its complete separation from other ingredients of a compound medicine is practically impossible.

If the product under examination contains no great amount of resinous matter and the proportional amount of volatile oil in the whole is large, it is quite probable that the oil and not the oleoresin has been employed. If the volatile oil contains caryophyllene and this sesquiterpene can be separated by means of its hydrate or some other derivative and its identity established, and if the absence of clove oil is established, and furthermore, if the volatile oil does not give the color reaction for gurjun, it is safe to assume that copaiba and not gurjun is present.

Copaiba is incorporated into pills and tablets in the form of copaiba mass or solidified copaiba, which is obtained by mixing the oleoresin with magnesium or calcium oxide and water. This mass may contain 90 per cent or more of the oleoresin. In pills and tablets the copaiba mass will run from $\frac{1}{2}$ grain up to 2 or 3 grains. In capsules the oleoresin may run from 3 to 10 minims. No satisfactory method for the determination of copaiba in medicines can be offered. An approximate estimation of the amount present can, however, be made with a fair degree of accuracy by one who has considerable experience with copaiba mixtures, but this is due more to the personal equation and cannot be set down in black and white.

AMMONIACUM

True or Persian.—Ammoniacum is the gum resin of Dorema ammoniacum (Umbelliferæ) which is a native of Persia, Northern India, and Southern Siberia.

It is used as an expectorant, stimulant, and antispasmodic in chronic catarrh, asthma, and bronchial affections, and is often combined with ipecac and squill in pills and tablets. It also has some reputation as an emmenagogue and diuretic. It is used externally for treating indolent ulcers and white swelling of joints, and is applied in plaster form as a rubefacient for chronic rheumatism.

The natural gum-resin consists of 60-70 per cent of acid and neutral resin, soluble in ether, a considerable portion (12–30 per cent) of gum, volatile oil, free salicylic, acetic, and caproic acid, water and vegetable débris. The acid resin is a salicylic ammoresinotannol ester, and the

isolated ammoresinotannol appears to be closely allied to galboresinotannol. The gum is similar to acacia and yields on hydrolysis galactose, arabinose, mannose, and an acid. Oxidation with nitric acid yields mucic acid and galactose, but not saccharic acid. The volatile oil has *n.* 1.4747–1.4808, and give the color reaction with sodium hypobromite described below. This oil has a specific gravity .891 at 150° and melts principally between 250–290°. Its odor is similar to that of angelica. Umbelliferone and sulphur are not present.

Ammoniacum occurs in irregular, rounded tears, yellowish outside and whitish within; opaque, brittle when cold, but soft when warm. It also occurs in masses darker in color and less homogeneous. The odor is peculiar and the taste is sweetish, bitter, and somewhat acrid. The masses contain a large quantity of volatile oil and are greasy, while the tears are solid. The gum resin, owing to its composition, is partially soluble in alcohol and water.

African ammoniacum is much darker in color and differs in taste and odor. It differs from Persian ammoniacum in proximate analysis and contains umbelliferone.

Adulteration with galbanum and African ammoniacum has been practiced. Other resinous and vegetable material are also used to sophisticate the pure product.

An alcoholic solution of ammoniacum gives a violet color with sodium hypochlorite and hypobromite. This test being of value in establishing the identity of ammoniacum in medicines and when mixed with other gum-resins.

Dieterich records the following constants for commercial ammoniacum:

Ash up to 10 per cent.

Loss at 100° C., 2.15–12 per cent.

Volatile acid value, 100–200.

Acid value ind., 90–105.

Resin value, 99.4–155.4.

Gum value, 7.0–46.2.

Total saponification value, 145.6–162.4.

A good ammoniacum shows a high volatile acid value and a low gum value.

African Ammoniacum tested by Dieterich showed the following figures:

Acid value ind., 47.59–92.21.

Resin value, 103.89–104.59.

Total saponification value, 105.3–108.1.

In general the values are lower than those given by Persian ammoniacum.

Dieterich's Methods for Assaying Ammoniacum.—The drug should be thoroughly chilled and ground in a cold mortar.

Volatile Acid Value.—0.5 gram is mixed with a little water in a flask, through which a current of hot steam is passed, the flask being heated in a sand-bath. The receiver contains 40 mils of N/2 KOH, into which dips the tube coming from the condenser. Five hundred mils are distilled and the excess alkali titrated back in presence of phenolphthalein. The number of mils of KOH combined, multiplied by 28.08 gives the volatile acid value referring to 0.5 gram.

Acid Value Ind.—One gram is boiled under a reflux with 50 grams water for fifteen minutes, followed by 100 grams alcohol for an equal time. After cooling the weight is made up to 150 grams, filtered and 75 grams of filtrate (0.5 gram of substance) are treated with 10 mils of N/2 alcoholic KOH, allowed to stand exactly five minutes and titrated back with N/2 sulphuric acid and phenolphthalein. The number of mils of combined KOH multiplied by 28.08 and referred to 1 gram of the substance gives the acid value.

Resin Value and Gum Value.—Two samples of 1 gram each are used. Each sample is treated in a 1000-mil stoppered flask with 50 mils petroleum ether (sp. gr. .700) followed by 25 mils N/2 alcoholic KOH, which is allowed to act in the cold for twenty-four hours, agitation being frequent. One sample is then treated with 500 mils of water and titrated back with N/2 sulphuric acid and phenolphthalein—this gives the resin value. The second sample is treated with 25 mils of N/2 aqueous KOH and 75 mils water and left, with frequent agitation twenty-four hours, then diluted with 500 mils of water and titrated with N/2 sulphuric acid, the result being the *total saponification value.* The respective quantities (mils) of KOH consumed multiplied by 28.08 gives the corresponding values.

The *gum value* is found by subtracting the resin value from the total saponification value.

Test for Galbanum.—Five grams are boiled with 15 mils strong hydrochloric acid for fifteen minutes, filtered until clear filtrate is obtained and then supersaturated with ammonia. If umbelliferone is present the liquid will show the characteristic blue fluorescence in reflected light.

The actual gum present can be determined approximately by dissolving 1–2 grams of the sample in sufficient 60 per cent chloral hydrate solution and pouring into 100–150 mils of 95 per cent alcohol. The precipitated gum is collected on a tared Gooch, washed with alcohol and weighed.

GALBANUM

Galbanum is the gum-resin of Peucedanum galbanifluum P. rubricaule and allied species of Umbelliferæ, indigenous to Persia

It is employed medicinally as a stimulant, carminative, and expectorant, chiefly in chronic affections of the mucous membranes, bronchial, uterine, and vaginal catarrh, and is offered in pill form combined with

myrrh and asafetida. Externally it is used as an irritant and mild stimulant in plasters.

Galbanum consists of from 10–20 per cent volatile oil, 50–67 per cent resin, 15–20 per cent gum, mineral matter and vegetable débris. The resin is soluble in ether and alkalies, and contains about .25 per cent free umbelliferone, galboresinotannol, and about 20 per cent umbelliferone combined with the resinotannol. The volatile oil has an aromatic and not unpleasant odor, yellowish in color, sp. gr. .910–.940 (.908–.955 Harrison and Self) and is reported as dextrogyrate up to +20° and lævo up to −10°. n=1.4863–1.4869. It is reported as containing *d*-pinene and cadinene, the latter being identified by the preparation of its hydrochloride, melting 117–118°. On dry distillation galbanum yields a blue oil having the odor of chamomile. On fusion the resin yields resorcin and an acid.

Galbanum occurs in agglomerated tears or masses, grayish yellow or greenish, with a wavy luster. The odor is balsamic and the flavor bitter, acrid, and burning. It is partially soluble in water, alcohol, and ether. When boiled with hydrochloric acid, filtered, and supersaturated with ammonia, a blue color, due to umbelliferone, appears.

Galbanum is often adulterated with ammoniacum, turpentine, fatty oils, sand, exhausted galbanum, and vegetable material.

Dieterich's researches on galbanum showed the following constants:

Volatile acid value, 73.5–114.

Acid value ind., 21.24–63.45.

Resin value, 107.5–122.5.

Total saponification value, 116.2–135.8.

Gum value, 8.4–16.1.

Ash, 8.4–16.1 per cent.

Loss at 100°, .35–31.5 per cent.

Galbanum should be assayed by the methods described for Ammoniacum. The quantity of the gum is determined by the precipitation of a chloral hydrate solution with alcohol.

Dieterich concludes that adulteration with ammoniacum decreases the volatile acid value, while asafetida has the reverse effect. Asafetida is readily detected by the characteristic odor during distillation. The indirect acid value is raised by ammoniacum but is reduced by asafetida. The presence of ammoniacum is indicated by the color reactions given with sodium hypochlorite and sodium hypobromite.

GAMBOGE

Gamboge is a yellow gum resin from Garcinia morella (Clusiaceæ) indigenous to Siam and Ceylon.

It is a valuable cathartic and is often found in combination with other drugs in remedies for obstinate constipation, intestinal torpidity and

hepatic troubles. The U. S. P. compound cathartic pills contain gamboge, jalap, colocynth comp. and calomel; other pill formulas consist of gamboge with aloes, Podophyllum, Capsicum and croton oil; with colocynth comp., jalap, ginger, rhubarb, and calomel; with jalap, Leptandra, aloin, Podophyllum, Capsicum, Hyoscyamus, peppermint; with aloes, colocynth, soap, and anise; with Veratrum viride, croton oil, aloes, jalap Podophyllum, Capsicum, and Leptandra.

Gamboge consists of resin, gambogic acid, gum, wax, and vegetable débris. The resinous material amounts to 75–82 per cent, the gum about 16 per cent. No volatile oil is present. It occurs in the trade in the form of pipes, cakes, lumps, and powder. The color is reddish yellow and the dry lumps have a chonchoidal lustrous fracture. It floats on carbon bisulphide at a temperature of 20° C. but sinks at higher temperatures. It is soluble in alkalies, and 60 per cent chloral hydrate, forms a yellow emulsion with water, partly soluble in alcohol, ether, and other volatile solvents.

Gamboge is often adulterated with colophony and in the powdered form was formerly almost never found free from admixture with starch. Other impurities consist of sand, dirt, dextrin, turmeric, and Taylor reports an instance of dangerous sophistication with lead chromate. Starch is almost always present in small quantity in powdered gamboge which is otherwise pure and the reason for the presence of minute quantities which can hardly be considered as intentional adulteration is not apparent. The mineral matter (ash) of pure gamboge should not exceed 1 per cent.

Starch may be detected by boiling some of the powdered drug with water, cooling, and adding iodin. A faint-green color will often appear at this juncture, but any color darker than this indicates adulteration. Eberhardt recommends boiling 1 gram of the powdered material with 5 per cent potassium hydroxide solution, neutralizing with acid, filtering, and testing the filtrate with iodin. There are certain advantages to the last procedure as the blue color of any starch iodide formed is not altered by the yellow pigment of the gum-resin; 2 per cent or over of starch will yield a blue precipitate.

Good gamboge should contain not more than 25 per cent of material insoluble in 95 per cent alcohol.

Taylor [1] determines both the alcohol-soluble portion of the gum resin and the acid value with one sample. Two grams of the powdered sample are digested with heat under a reflux condenser with exactly 150 mils 95 per cent alcohol for not less than fifteen minutes, the solution cooled and 75 mils (representing 1 gram of the resin) filtered off through a dry tared filter. This 75 mils is used for titration of the acid value, which is

[1] J. Ind. and Eng. Chem., 1910, II, 208.

made direct on this solution, and the filtration is continued so that the insoluble residue may be finally collected in the filter and weighed. The acid value titration gives results agreeing with those obtained by Dieterich's method.

The acid value runs from 80–96 and this value varies in direct proportion to the alcohol solubility with few exceptions. In other words, a high alcohol solubility usually accompanies a high acid value. Some of Taylor's figures illustrative of this relationship are appended.

Acid Value	*Alcohol Solubility*	
95.8	84.0	all pure gamboges
91.6	79.05	
88.6	82.0	
85.8	77.4	
85.8	77.0	
81.6	74.9	
80.2	76.15	
80.5	52.95	starch adulterant
67.7	57.6	colophony adulterant
67.7	61.3	colophony adulterant

Dieterich's method for determining the resin value and total saponification value:

Two 1-gram samples of finely triturated gamboge are each covered with 25 mils N/2 alcoholic KOH and allowed to stand tightly stoppered for twenty-four hours. One sample is then diluted with water and titrated, the volume of the KOH consumed multiplied by 28.08 giving the resin value. The second sample is then treated with 25 mils N/2 aqueous KOH, allowed to stand twenty-four hours longer and titrated, the result giving the saponification value. The gum value is obtained by difference.

Dieterich found the resin value to run from 105–116.2; the total saponification value from 121.8–138.6, the gum value from 14–22.4

The percentage of gum may be determined by Mauch's method. The sample is dissolved in 5 parts of 60 per cent aqueous chloral hydrate, precipitated by alcohol, and the gum collected on a tared Gooch, washed with alcohol and weighed.

LACTUCARIUM

Lactucarium is the dried milky juice of Lactuca virosa (Compositæ) and other species of Lactuca. It is obtained by cutting off the tops of the stems and when the latex which exudes is partially hardened, it is collected and dried in hemispherical earthen cups until it can be cut into pieces and which are usually four in number, these being further dried.

It occurs in commerce in irregular, angular pieces or quadrangular sectors. one surface of which is convex, externally dull reddish or grayish

brown; fracture tough, waxy, internally light brown or yellowish, somewhat porous, odor distinct and opium-like, taste bitter.

It is partly soluble in alcohol, ether, chloroform, and water.

Three bitter principles are reported as occurring in lactucarium, lactucin, which occurs in white rhombic prisms, sparingly soluble in water; lactucopicrin, a brown, amorphous, very bitter principle which is readily soluble in water and alcohol; and lactucic acid, a yellow, very bitter substance crystallizing with difficulty and colored red by alkalies. It contains also about 50 per cent of a colorless, odorless, and tasteless crystalline substance, lactucerin (lactucon); α- and β-lactucerol in the form of acetates, volatile oil, mannitol, organic acids, citric, malic, and oxalic.

The principal use of lactucarium is in a certain class of anodyne syrups recommended for infants. It may be combined with opium in these remedies. It also enters into the composition of some syphilitic pills with mercurous iodide, opium, and Conium.

The commercial varieties include German and English lactucarium and Lactucarium Gallicum from L. sativa, the " Thridax " of ancient days.

German lactucarium forms tough, homogeneous, yellow-brown masses, somewhat waxy in fracture and hygroscopic. The English drug consists of irregular, larger, and smaller granules, more or less obtuse angled, dull, friable, dark brown in color and non-hygroscopic. Gallicum is a blackish-brown fatty extract.

Lactucarium is adulterated with farinaceous material, vegetable extracts, and colophony.

The important constants of lactucarium are determined by Dieterich as follows:

Two 1-gram samples of the powdered drug in stoppered liter flasks are covered with 50 mils petroleum ether (sp. gr. .700) followed by 25 mils N/2 alcoholic KOH, and allowed to stand for twenty-four hours with frequent shaking. One sample is then diluted with 500 mils of water and titrated back with N/2 sulphuric acid, the results giving the *resin value.* The second sample is further treated with 25 mils of N/2 aqueous KOH and 75 mils water and allowed to act with occasional agitation twenty-four hours longer. It is then diluted with 500 mils of water and titrated back with N/2 sulphuric acid, the results giving the *total saponification value.* The *gum value* is determined by difference.

For German lactucarium in mass Dieterich found resin value 154–156.8; total saponification value 166.6–169.4; gum value 12.6. High resin and saponification values indicate adulteration with colophony which should be tested for by the Storch-Morawski reaction.

The results Dieterich obtained on the English drug indicated irregular composition; resin value from 50.4–225.4; saponification value 75.6–238; gum value 7–26.6. It is probable that the excessively high data

for resin and saponification values were obtained with sophisticated products.

MYRRH AND ITS ALLIED GUM RESINS. (HERABOL MYRRH)

Myrrh is the dried emulsion-like juice which exudes from several species of Commiphora and Balsamodendron (Burseraceæ), native in the coast districts of the Red Sea such as the Somali coast of East Africa, in Arabia, and probably Persia. From the interior of the Somali lands there comes a variety of myrrh (bisabol) which has been ascribed to Balsamea erythrea, belonging to the same family, and which has been considered identical with commercial opopanax. The latter drug occurs in two varieties, the burseraceous and umbelliferous, the former being found in the trade, and its source has been ascribed to the species Balsamodendron kafal. As a matter of fact the botanical origin of these gum resins has not been traced with entire satisfaction and any statements regarding the species yielding the burseraceous gum-resins must be taken with reserve.

Herabol myrrh is the usual commercial grade. It has a wide and varied use in medicine, for besides being a valuable constituent of mouth washes, tooth powders, and applications for spongy gums and sore throat, it is a stimulating tonic with apparently some influence on the lungs and uterus and is found in female pills, liquid aloes mixture, expectorants, etc. Myrrh is combined with aloes and licorice in fluid compounds of aloes, and also with Capsicum. It also accompanies aloes in many different pill formulas. Female pills contain myrrh, aloes, ferrous sulphate, hellebore, ginger, soap, and Canella. Other formulas containing myrrh include asafetida and galbanum; rhubarb, aloes, soap, and peppermint; aloes and mercury mass; aloes, scammony, croton oil, and caraway. Warburg tincture contains myrrh. Astringent mouth washes contain myrrh combined with glycerin and mild antiseptics and aromatics. Tooth powders often contain myrrh. Griffith's mixture, the compound iron mixture, consists of myrrh, ferrous sulphate, sugar, potassium carbonate, and flavors. The volatile oil of myrrh is employed as a remedy for bronchitis. Plasters contain myrrh, camphor, Peru balsam, and lead oleate.

Herabol myrrh occurs in the form of masses and granules, yellowish red in color, with a greasy, lustrous, fine-grained fracture. It has a strong and characteristic odor and a bitter acrid taste. It forms a milky emulsion with water and alcohol dissolves the resinous portion. This drug is the so-called "male myrrh." It consists of 50–75 per cent of gum; 2.5–8 per cent of volatile oil, 20 per cent or more of resin. The presence of a bitter principle has been reported. The resin is a complex mixture containing neutral resin and resinous acids. The volatile oil has sp. gr. .988–1.007; $(\alpha)_D = -67°$ to $-90°$, and its solution in petroleum ether is

colored red by bromine vapors, a test which distinguishes this variety of myrrh from Bisabol myrrh and bdellium. The ash should not exceed 8 per cent.

Myrrh is adulterated with Bisabol myrrh, bdellium, gum arabic, and extracted myrrh resin.

If Herabol myrrh is treated with petroleum ether (1–15), and six drops of the clear extract are mixed with 3 mils of glacial acetic acid and floated on the surface of 3 mils of concentrated sulphuric acid, the acetic layer develops a very pale rose color which does not increase in strength, and the surface of contact between the two layers shows at first a green color which turns brown with a green fluorescence on standing. With Bisabol myrrh a rose red zone immediately forms at the surface of contact and the coloration soon extends throughout the entire layer of acetic acid and remains persistent.

Dieterich gives the following methods for determining the constants of myrrh:

Acid Value.—One gram of the finely powdered myrrh is treated with 30 mils of distilled water and warmed for fifteen minutes under a reflux, 50 mils of 95 per cent alcohol are added and the boiling repeated for fifteen minutes. After cooling the liquid is titrated with N/2 alcoholic KOH and the volume of alkali consumed multiplied by 28.08 gives the acid value.

Saponification Value.—One gram of the sample is treated with 30 mils of water, allowed to stand one-half hour, treated with 25 mils N/2 alcoholic KOH and boiled for one-half hour under a reflux on the steam-bath. After cooling and diluting with alcohol it is titrated back with N/2 sulphuric acid, the volume of alkali consumed multiplied by 28.08 gives the saponification value.

Ester Value.—This is found by difference.

Alcohol Soluble.—Determined by extracting the sample with 95 per cent alcohol in a thimble in a Knorr or Soxhlet apparatus and weighing the undissolved portion.

Dieterich reports the following values for myrrh and the allied gum-resins.

	Acid Value	Ester Value	Saponification Value	Solubility in Alcohol, Per Cent
Herabol myrrh.....	25.48	204.12	229.60	20
Bisabol myrrh.....	20.06	125.54	145.60	50
African bdellium....	9.73–20.8	70–96	82–111	
Indian bdellium.....	35.6–37.19	46.75–48.46	82.44–85.65	
Burseraceous opopanax	10.46–30.92	81.94–97.24	96.20–152.82	
Umbelliferous opopanax	32.43–58.57	105.46–142.6	137.89–199.07	

The percentage of gum in myrrh is determined by Mauch's method. One to two grams of the sample are dissolved in 10–15 grams of 60 per cent aqueous chloral hydrate and precipitated with 100 grams 95 per cent alcohol. The precipitate is collected on a tared Gooch, washed with alcohol, and weighed.

Bisabol myrrh contains a much smaller percentage of gum and a larger quantity of resin than Herabol myrrh. It contains a bitter principle, water, volatile oil, and vegetable débris. The resin contains free acids, a resene, and a neutral substance. This drug is known as " female myrrh."

BDELLIUM

African bdellium is probably derived from Commiphora africana, and East Indian bdellium from Balsamodendron indicum (Burseraceæ). The African drug is in reddish oval or round lumps about ½ inch across, which have a greasy luster, and become soft and plastic when warmed. East Indian bdellium is in the form of shapeless agglomerated lumps about one inch in diameter, externally rough, uneven, dull, of a dark-brown color, a lustrous fracture, a sharp, bitter flavor and an odor resembling Bisabol myrrh. Bdellium furnishes a white emulsion with water like myrrh. It does not give the characteristic color reactions of myrrh with bromin vapor and its analytical constants are different. Our interest in the drug is chiefly on account of its being used as an adulterant of myrrh, and the methods of examination are precisely the same as detailed under that drug.

Indian bdellium is employed in the East as a remedy for leprosy, syphilis, and rheumatism.

OPOPANAX

There are two distinct varieties of this gum-resin, one derived probably from Balsamodendron kafal (Burseraceæ) of Persia and the other from Cheronium opopanax (Umbelliferæ) of Southern Europe.

The Burseraceous gum-resin consists of about 19 per cent of resin, gum, and vegetable débris up to 70 per cent, volatile oil 6–10 per cent, and moisture. The resin consists of α-panaxresene ($C_{32}H_{54}O_4$); β-panaxresene ($C_{32}H_{52}O_5$); panaxresinotannol ($C_{34}H_{50}O_8$); an alcohol, chironal ($C_{28}H_{48}O$), and bitter principle. The oil has a greenish color and a pleasant balsamic odor. It resinifies readily on exposure to air, specific gravity 0.870-0.905; $(\alpha)_D - 10 - 12°$. With bisulphite solution a brownish mass separates from the oil, which on sublimation yields white needles melting 134-134°, to which the name oponal ($C_{20}H_{10}O_7$) has been given.

This variety of opopanax is commonly designated as myrrh in the East and according to Holmes may probably be the myrrh of the Scriptures. Its odor is peculiar, resembling Sumbul and Bisabol myrrh. It

occurs in large, brown yellow lumps with paler gummy granules and smaller white lumps.

The chemical constants have been recorded under myrrh and may be determined by the same methods.

Umbelliferous opopanax has a strong disagreeable odor and balsamic taste. An analysis showed 51.8 per cent ether-soluble resin (ferulic acid ester of oporesinotannol); 19 per cent ether-insoluble resin; 33.8 per cent gum; 8.3 per cent volatile oil, small quantities of ferulic acid, and vegetable residues. It occurs in greasy masses or brownish yellow lumps.

ASAFETIDA

This gum resin is a product of several species of Ferula (Umbelliferæ) the ninth revision of the U. S. P. designating F. asafetida and F. fetida as the chief sources. J. Small, who has examined the botanical sources of the fetid gum resins, assigns the white asafetida to F. rubricaulis and the red variety to F. fetida.

Asafetida is a component of sedative mixtures and remedies for whooping cough, chorea, chronic bronchitis, hysterical affections, convulsions, flatulent constipation, asthma, and catarrh. It is sometimes dispensed in liquid form, but more often in pills or tablets. Sedative mixtures will consist of asafetida with sumbul, valerian, ferrous sulphate, and arsenous acid. It will be found combined with aloes and soap; with opium and ammonium carbonate; with Nux Vomica; with reduced iron and rhubarb; and with myrrh and galbanum. Asafetida is very extensively employed in veterinary practice especially in remedies for " heaves."

At the time the Food and Drugs Act went into operation probably there was no imported drug which was so flagrantly adulterated as asafetida. The Pharmacopœia had prescribed a standard for the drug but no attention was paid to the requirements except by a few progressive manufacturing pharmacists. In general the importer paid little attention to the quality of the drug. The change in conditions after January 1, 1907, caused a storm of protest from the importers of asafetida, and it was some time before the authorities could convince them that the standards of the Pharmacopœia were reasonable, and were based on the examination of specimens of known purity. At that time the asafetida was adulterated with sand, gravel, and broken lumps of mineral matter, and the ash frequently ran over 50 per cent. Other gums and gum resins, galbanum, African ammoniacum, rosin, and turpentine were also used, and after the more easily detectable mineral matter ceased to be a source of trouble, the sophistication with other resinous material persisted and still does.

A peculiar gum resin of uncertain origin, known to the trade as pepper

asafetida, should not be mistaken for the official drug. Its odor is similar when cold, but on heating a pungent, peppery odor develops which is not characteristic of true asafetida. The lead number is low, 82.

Asafetida consists of about 62 per cent of the ferulic acid ester of asaresinotannol, small amounts of free ferulic acid and asaresinotannol, about 25 per cent of gum, 3–17 per cent of volatile oil, a trace of vanillin, moisture, and mineral matter, the latter amounting to not over 10 per cent in a good crude drug.

The steam-distilled oil possesses the disagreeable, alliaceous odor of the drug. It has specific gravity .975–.990; n 1.4942–1.5250; $(\alpha)_D - 9° 15'$ (Gildermeister and Hoffman), $-35° 55'$ to $+9° 39'$ (Harrison and Self). It contains two terpenes, one identical with pinene, and several sulphur compounds which were fractioned by Semmler, and found to be a disulphide $C_7H_{14}S_2$, boiling 83–84° at 9 mm.; sp. gr. 0.9721 at 15°; $(\alpha)_D - 12° 30'$, comprising about 45 per cent of the crude oil.

A disulphide, $C_{11}H_{20}S_2$, sp. gr. 1.0121; boiling 126–170° at 9 mm.; $(\alpha)_D - 18° 70'$, comprising 20 per cent of the oil and being the cause of the repulsive odor of the drug.

A substance $(C_{10}H_{16}O)n$, sp. gr. .9639 at 22°; boiling 133–145° at 9 mm.; $(\alpha)_D - 16°$ present to the amount of 20 per cent and yielding cadinene, $C_{15}H_{24}$, on treatment with sodium.

A compound, $C_8H_{16}S_2$, boiling 92–96° under 9 mm.

A disulphide, $C_{10}H_{18}S_2$, boiling 112–116°.

Harrison and Self consider this oil, and especially its sulphur content, an important factor in the valuation of the drug and their method of procedure is subsequently described.

Pure asafetida will show acid value 65–80, ester value 80–130, saponification value 120–185, lead number 200 up, ash 1–10 per cent.

Analysis of Asafetida.—It is important to obtain a fair average sample of a lot of asafetida and poor sampling is usually the cause of divergent results in cases of contest. Several drawings should be made from a package and these thoroughly mixed and if possible run through a sausage grinder to ensure homogeneity.

Alcohol Soluble.—Introduce about 10 grams of asafetida into a tared, 250 Erlenmeyer flask, determine the exact weight of the drug, add 100 mils of alcohol, and having connected the flask with an upright condenser, boil the mixture in the flask during one hour or until the drug is completely disintegrated. Then transfer the contents of the flask to two counterpoised, plainly folded filters, one within the other, so that the triple fold of the inner filter is laid against the single side of the outer, and wash the flask and filter with consecutive, small portions of boiling alcohol until the washings no longer produce a cloudiness when dropped into water. Collect and reserve the mixed alcoholic solutions, for the qualitative tests

given below. Dry the filters and flask to a constant weight at a temperature of about 115° C. Now determine the weight of the residue on the filter and in the flask and calculate its percentage from the amount of asafetida originally taken. This percentage of alcohol-insoluble material, when subtracted from 100, gives the percentage of alcohol-soluble constituents contained in the asafetida.

Acid Value. (Dieterich).—One gram is treated with 10 mils each of N/2 alcoholic and aqueous KOH, and left to stand in a stoppered liter flask for twenty-four hours at room temperature. After dilution with 500 mils of water, the whole is titrated back with N/2 sulphuric acid. The volume of KOH consumed multiplied by 28.08 gives the acid value.

Saponification Value. (Dieterich).—One gram is treated with 25 mils N/2 alcoholic KOH and boiled for one hour under a reflux. At the end of that time 200 mils of alcohol are added and when cold the whole is titrated back with N/2 sulphuric acid. The volume of KOH consumed multiplied by 28.08 gives the saponification value.

The ester value is determined by difference.

Gum Assay.—One to two grams of the sample are dissolved in 10–15 grams of 60 per cent chloral hydrate filtered from mineral matter, the filter washed with the reagent and the gum precipitated by pouring the mixture into 10 parts of 95 per cent alcohol. The precipitate is collected on a tared Gooch, washed with alcohol, dried and weighed.

Ash Determination. Mauch's Method.—The sample is treated with ten to fifteen times its own weight of 60 per cent chloral hydrate solution, filtered onto an ashless filter, washed with chloral hydrate solution followed by alcohol, dried and ignited.

Determination of Sulphur in Asafetida Oil.—Harrison and Self [1] determine the amount of sulphur in the volatile oil and refer the figure thus obtained to the amount of real gum resin in the drug. Therefore, account must be taken of the ash content. They claim that the amount of sulphur should not be below 1.5 per cent on the gum resin basis and may run to 4.04 per cent.

A weighed amount of the drug is subjected to steam distillation and the oil collected. The oil is separated and dried, 0.5 gram is weighed into a flask of 150 mils capacity fitted with a ground-in condenser; 5 mils of water are added, followed by 5 mils of nitric acid, sp. gr. 1.42. The flask is gently warmed to start the reaction, 3 grams of potassium bromide are then added, the whole boiled for ten minutes, cooled and treated with 5 grams of sodium hydroxide dissolved in a little water. The contents of the flask are evaporated to dryness and ignited in a platinum crucible. After dissolving in water, the nitric and nitrous acids are boiled off and the sulphur determined by precipitation with barium chloride in presence

[1] Pharm. J., 1912, 88, 205.

of hydrochloric acid. A blank determination with materials used must also be made.

If there is a large percentage of volatile oil and a small percentage of sulphur the presence of terpenes is indicated. Admixture of galbanum, olibanum, and ammoniacum lower the percentage of sulphur in the gum resin as these drugs contain no sulphur in the oil. Volatile oil of ammoniacum has *n.* 1.4747–1.4808, and as an adulterant would lower the oil content. Galbanum has *n.* 1.4863–1.4869, 1.4840 (Sechler and Bechu), elemi has *n.* 1.4869. Both galbanum and elemi would lower the sp. gr. of oil of asafetida and increase the dextro-rotation, therefore decreasing the lævo-rotation. Galbanum contains umbelliferone, which can be detected by the blue fluorescence produced by alcoholic ammonia. Asafetida yields the blue fluorescence after boiling with hydrochloric acid, but olibanum and ammoniacum do not.

LEAD NUMBER. (E. C. MERRILL)

This method was proposed by H. A. Seil and was developed by Merrill and reported in the Journal of the A. O. A. C., Vol. II, No. 1, page 83.

Use a sample (about 20 grams) sufficient to furnish between 5 and 10 grams of the ether purified resin. Determine the alcohol insoluble material in the usual manner. Transfer the first 2 filtrates, representing the major part of the sample, to a casserole or a flat-bottomed porcelain dish, and evaporate the alcohol on the steam-bath. Treat the resinous mass with ether (sometimes it is necessary to warm gently to facilitate solution of the resin). Filter the ethereal solution into a separatory funnel and wash with water until the aqueous layer separates without any milkiness. (If the ether solutions persist in remaining turbid, more ether may be added, or it may become necessary to dry the ether solution by shaking with sodium chloride in the separatory funnel after as much as possible of the aqueous solution has been removed.) Then filter the ethereal solution through a folded filter paper, moistened with ether, into a flask or beaker, and evaporate the solvent on the steam-bath.

Determination.—(The residual ether purified resin from the above preparation is now in a state where it can usually be broken up when cold, and powdered.)

Into a small tared beaker (about 75-mils capacity) weigh roughly about 1.1–1.2 grams of the resin prepared above and dry for five hours in the air-bath at 110° C. Place in a desiccator, cool, and weigh. (The weight noted is to be used in subsequent calculations.) Dissolve in 20 mils of 95 per cent alcohol, boil gently until the resin is in solution, transfer to a 100-mil graduated flask, wash the beaker with hot 95 per cent alcohol, care being taken that the final volume does not exceed 70 mils.

Add 25 mils of the alcoholic lead acetate, agitate and allow to stand overnight. Make up to the mark with 95 per cent alcohol, shake well, allow to stand a few minutes, and then filter through a fluted paper and pipette an aliquot of 25 mils from the filtrate into a beaker. Add 10 mils of water and evaporate to 10 mils. Add 5 mils of 10 per cent sulphuric acid and then 100 mils of alcohol, stirring vigorously to dissolve any separated resin, and heat if necessary. Allow to stand for an hour, then filter the lead sulphate on a tared Gooch, wash with alcohol and finally with ether, dry at 100° C. to a constant weight and weigh.

Run a blank on the alcoholic lead acetate solution, and calculate the amount of metallic lead absorbed by 1 gram of the dried resin. The mg. of lead per gram of sample represent the lead number. The factor for the conversion of lead sulphate to metallic lead equals 0.6830.[1]

The lead numbers of a number of authentic resins and gum resins determined by Merrill showed asafetida 222, galbanum 4, ammoniacum 75, olibanum none, guaiac 171, myrrh 7, colophony 142, bdellium 55, sandarac 251, mastic 34, gamboge 9. dragon's blood, none, euphorbium 34, pepper asafetida 82.

Qualitative Test for Colophony (Merrill).—For this test Merrill recommends using about 40 mils of the alcoholic solution obtained in determining the alcohol-soluble matter. Transfer to a separatory funnel, add 30 mils petroleum ether, mix, add 50 mils of water and shake for thirty seconds. After separating, discard the aqueous milky layer. Wash the petroleum ether layer with water until the wash water and petroleum ether are both clear. Add 30 mils of 0.5 per cent copper acetate solution and shake well. No green color should appear in the petroleum ether. The appearance of a green color indicates the presence of foreign resins.

SAGAPENUM

This gum resin is derived from a botanical source not yet satisfactorily identified but belonging to the Umbelliferæ. It contains a volatile oil containing sulphur compounds, and its odor recalls both asafetida and galbanum. It contains a considerable portion of resins soluble in ether which has been found to consist of free umbelliferone and umbelliferone-sagaresinotannol ester. Its ethereal solution gives a red-violet color with hydrochloric acid. Like galbanum it gives the umbelliferone reaction.

[1] For the preparation of alcoholic lead acetate dissolve 5 grams of normal lead acetate in 20 mils of water and add 80 mils of 95 per cent alcohol. A turbidity generally results, due to the precipitation of lead carbonate caused by carbon dioxide in the alcohol. Allow the solution to stand overnight. The clear, supernatant liquid can then be used without filtering for the determination of the lead number.

The blank on 25 mils of alcoholic lead acetate solution should be equivalent to at least 1 gram, calculated as $PbSO_4$.

Its assay may be conducted by the procedure given under Myrrh and Dieterich has obtained the following values:

Acid value, 13.96–14.81.

Ester value, 31.29–39.37.

Saponification value, 45.25–54.18.

RUBBER AND CHICLE

A detailed consideration of the chemistry of rubber and its uses is not within the scope of this work, but reference will be made to its composition and general characteristics for it will be encountered in testing plasters and chewing gums where it often functionates as a basic component. In connection with rubber it is in order to discuss the characteristics of chicle, the chemistry of which is allied to that of rubber. The sources of rubber and chicle, as well as gutta percha and balata, are the milky juices or latices of a number of different trees, shrubs, and vines. The latices consist of watery emulsions holding in suspension minute globules of material, which coagulate under proper treatment and produce the commercial articles.

The coagulated materials consist chiefly of hydrocarbons and resins with more or less carbohydrates, gums, proteids, tannins, mineral substances, coloring matter, and water. The resinous constituents may be oxidation products of the hydrocarbons as it has been found that when the pure hydrocarbons are separated and purified, they take up oxygen with ease.

The fundamental hydrocarbons are multiples of $C_{10}H_{16}$, and the hydrocarbons separated from all four sources are apparently closely allied, if not identical, that from rubber is designated caoutchouc, that from gutta percha as gutta and the corresponding hydrocarbons from balata and chicle are termed bala-gutta and chicle-gutta.

The latex yielding rubber is secreted by many different botanical species representing several families among which may be mentioned the Euphorbiaceæ, Urticaceæ, Apocynaceæ, and Asclepiadaceæ. Gutta percha, balata, and chicle are obtained chiefly from latices of species of the Sopotaceæ.

Raw or unvulcanized rubber is soft, pliable, and elastic, at the ordinary temperature. When heated with boiling water or by mechanical working it becomes still softer. It is insoluble in water but is capable of absorbing up to 25 per cent of its own weight. It is insoluble in absolute alcohol but forms solutions with chloroform, benzol, toluol, carbon tetrachloride, carbon bisulphide, petroleum distillates, etc. Crude rubber contains a substance insoluble in the ordinary rubber solvents but which appears to swell up when subjected to their actions.

The rubber hydrocarbon is attacked by the halogens and other oxidizing agents. The oxidation product with ozone is a viscid substance which solidifies to a glassy explosive solid.

CHICLE

This coagulum from the latex of Achras Sapota is usually called gum chicle which is technically a misnomer, as the product comes under the class of gum resins and the resinous portion predominates.

It forms a tenacious, firm, aromatic, and elastic mass, white or reddish in color. The red color sometimes develops when the latex is overcooked in the process of concentration, but this is not always the case as some trees yield a gum-resin with a distinctly red color.

Reports of the composition vary. Dieterich found 75 per cent resin, 10 per cent gum, 9 per cent calcium oxalate, 5 per cent sugar and organic salts.

Berry [1] states that the resins run from 35.6–55.78 per cent, hydrocarbons 10.39–13.84 per cent. He separates the resins into two groups, resin *A* insoluble in cold absolute alcohol, saponification value 129; and resin *B* soluble in cold absolute alcohol, saponification value 100.8. He found the saponification value of the combined resins to be 101.7–104. Acid value slight.

Taylor reports an acid value of 52, no ethers or esters, 0.2 per cent ash, 82.7 per cent soluble in chloroform and 84.7 per cent soluble in benzol.

Tschirch,[2] in his systematic manner, has examined chicle and reports 16.8 per cent soluble in boiling water, 59.7 per cent in boiling alcohol, 61.7 per cent in boiling acetone, 76.2 per cent in boiling ether, and 77.2 per cent in chloroform.

He treated chicle successively with boiling water, boiling alcohol, and chloroform, and examined the fractions. The water soluble portions yielded 9 per cent of gum. In the alcohol-soluble portion was found α-chiclalban, $C_{24}H_{40}O$, melting 219–221°; β-chiclalban, $C_{18}H_{30}O$ or $C_{17}H_{28}O$, melting 158–159°; γ-chiclalban, $C_{15}H_{28}O$, melting 86–87°; and chiclafluavil, $C_{10}H_{18}O$ or $C_{10}H_{20}O$, melting 66–67°. In the chloroform portion was the hydrocarbon chiclagutta, $C_{10}H_{16}$ or $C_{10}H_{18}$, and chiclalbanan, an oxidation product, melting 55–57°.

CHEWING GUM

The principal components of chewing gum are chicle or some substitute, glucose, caramel, sugar, and flavor. Starch is often present in small quantity, as it is used in dusting the gum sheets to prevent their sticking to the rolls.

[1] Jour. Soc. Chem. Ind., 1904, 529.

[2] Arch. Pharm., 1905, 243–378.

Substitutes for chicle often comprise the base of chewing gum. They are usually prepared by mixing low-grade rubber, the resinous constituents of crude rubber, gutta percha, or balata, the resene portions of other resins such as dammar, and vegetable wax or paraffin.

Cauchillo gum is used as a masticatory similarly to chicle, and has been sold quite extensively to chewing gum manufacturers. It is of uncertain origin, but is reported to be derived from a tree in South America. It resembles chicle in physical appearance and is often denominated as chicle in the trade. Chewing gums are medicated with pepsin and to a lesser extent with strychnin or some other bitter substance. The latter type of product is used for the purpose of breaking up the tobacco habit. Occasionally one will meet with unusual mixtures having a chewing gum base, as instanced by one containing a large percentage of coca leaf and which was quite extensively sold several years ago.

A complete analysis of a gum includes determinations of the proportional amounts of the base, sugars, and medicament, a test for digestive power, the amount of moisture and other volatile components, and ash. As a general thing the drug analyst is concerned only with the medicinal constituents, and in the case of pepsin gums it is often only a question of determining whether or not the sample will act on coagulated egg albumin.

For the analysis several sticks of the sample should be broken up into small pieces and thoroughly mixed.

The moisture and volatile matter are determined with a 1–2 gram sample, drying at 100–110°. The residue is ignited and weighed as ash. Good chicle gum leaves an ash consisting chiefly of calcium carbonate, no sand or other gritty material being present.

To prepare a sample for determining the sugars, etc., about 5 grams are transferred to a flask or stoppered bottle, covered with chloroform and shaken until the resinous ingredients have dissolved. The solution is filtered, the insoluble substance washed with chloroform and then allowed to dry. The dry residue is digested with cold water, and filtered from any insoluble material. Solution may be hastened by transferring as much as possible to a small mortar and grinding the material in the presence of the solvent. The solution is finally made up to a definite volume and the sugars determined in the usual way.

An aliquot of the solution is then adjusted to the proper strength with hydrochloric acid, added to a bottle containing a weighed amount of egg albumin and a pepsin test conducted as described in the chapter on " Digestives." If digestive agents other than pepsin are suspected the appropriate procedure will necessarily follow.

If strychnin salts or those of other alkaloids are present they will be found principally in the aqueous solution though some portion will go into the chloroform. The alkaloids are freed from the aqueous solution

by making alkaline and shaking out with chloroform. From the chloroform solution containing the gum base, any alkaloids can be separated by shaking out with a little normal sulphuric acid and then removed from the acid by making alkaline and shaking out with chloroform.

F. J. Andress [1] employs a scheme for testing the gum base in which he masticates a weighed sample until the sugar and flavor have disappeared, dries it in an oven and then weighs. The procedure then goes ahead as follows:

Weigh off a 2 or 3-gram sample in an alundum extraction thimble, using a small cotton plug to close up the open end. Extract with acetone in a Soxhlet apparatus for five or six hours. Allow the extraction to proceed until the acetone becomes colorless as it siphons over and then continue the extraction until about ten more portions have been returned to flask. After the extraction is completed, disconnect the apparatus and dry thimble in steam oven to constant weight. Distill off the acetone in flask, dry in oven, and weigh.

Residue in Thimble.—If a pure chicle has been used, this will be a light reddish color and somewhat brittle. Should it, however, be a black, elastic body, substitution in all likelihood has been employed in the manufacturing process. To make a proper comparison, it is advisable to extract some pure chicle gum and compare the residues obtained.

Extract.—This may consist entirely of the resinous matter in chicle. It will also contain any wax or oil used in compounding the substitute or finished gum. Weigh off a 1-gram sample of the acetone extract, transfer to a 300-mil Erlenmeyer flask and determine the saponification value. Good results may be obtained by using 5 mils of benzene to take the resins into solution and then adding 20 mils N/2 alcoholic KOH for the saponification. Run a blank, using the same amounts of benzene and KOH. A funnel with the stem cut short is a very satisfactory reflux condenser.

Replace any alcohol lost in the boiling, adding the same amount to both flasks. One hour's boiling is usually sufficient to complete the saponification. Add 100 mils of cold water (recently boiled and cooled) 1 mil of phenolphthalein solution and titrate with N/10 HCl. Calculate the number of milligrams of KOH required to saponify 1 gram of resin. Most of the resins from the rubber gums likely to be used, will have a saponification value of 87 to 100 milligrams of KOH.

Waxes.—Use a 1-gram sample of the resinous extract. Warm with about 50 grams of glacial acetic acid. The resins, fatty matters, and mineral oils will go into solution, while the paraffin, on cooling, separates out almost quantitatively. Filter on a tared filter, wash three or four times with cold, glacial acetic acid and then follow with four or five washings with cold water, to remove the acid. Dry in steam oven and

[1] The Chemist Analyst, Nov., 15, 1916, page 5.

weigh. Use a stoppered weighing bottle in drying the filter and make the drying and final weighing in the same bottle, to prevent loss of wax, which in drying may melt and pass through the filter.

PLASTERS

Plasters consist of a medicament incorporated in a base of some resinous character and spread upon cloth or paper.

Plaster mass or the base on which the adhesive character depends, varies in composition. Among the combinations may be mentioned the following:

Rubber, Burgundy pitch and olibanum.

Lead oleate or lead plaster as it is commonly called.

Soap, lead plaster, and colophony.

Lead plaster, yellow wax, colophony, ammoniacum, myrrh.

Bdellium, olibanum, turpentine, and storax.

Individual plasters or those to which specific names are applied include:

Ammoniac plaster composed of ammoniacum and acetic acid

Aromatic plaster composed of lead plaster with cloves, cinnamon, ginger, capsicum, camphor, and cotton seed oil.

Camphorated Brown Plaster (Camphorated Mother Plaster) composed of lead oxide, olive oil, yellow wax, and camphor.

Galbanum plaster, composed of galbanum, turpentine, Burgundy pitch, and lead plaster.

Pitch plaster, composed of Burgundy pitch, olibanum, colophony, beeswax, and olive oil.

Canada pitch plaster, composed of Canada balsam and yellow wax.

Resin plaster, composed of colophony, lead plaster, and yellow wax.

Lead Plaster (diachylon) prepared with lead oxide and olive oil which yields practically lead oleate.

The plaster masses described above or the named types of plasters are employed in making up the various medicated plasters. The following list includes the principal forms of medicated plasters which will be encountered in analytical work:

Aconite with base of resin plaster.

Ammoniacum with mercury and oleate of mercury in a lead plaster base.

Arnica in resin plaster.

Asafetida in a base of lead plaster, galbanum, and yellow wax.

Belladonna in resin or soap plaster.

Capsicum in resin plaster.

Compound tar plaster composed of colophony, tar, Podophyllum resin, Phytolacca, and Sanguinaria.

Iron or Strengthening plaster composed of ferric hydroxide in Burgundy pitch and lead plaster.

Mercurial plaster, composed of mercury and mercury oleate in lead plaster.

Menthol in resin and beeswax.

Antimonial composed of tartar emetic in Burgundy pitch.

Opium in Burgundy pitch and lead plaster.

Cantharides, composed of cerate of cantharides and Burgundy pitch or powered cantharides in beeswax and soap plaster.

Lead iodide in lead plaster and resin.

Zinc plaster consists of zinc oleate and palmitate.

Mustard plaster consists of powdered black mustard deprived of its oil incorporated in a rubber base.

Adhesive plaster consists of rubber, resins, and waxes with a filler of absorbent powder such as orris root or starch.

Court plaster consists of a mixture of isinglass, glycerin, and benzoin.

Analysis of Plasters.—The analysis of a plaster of alleged composition for the purpose of identifying its medicinal constituents is neither difficult nor complicated. A detailed scheme which is both simple and accurate has been described in my work " The Qualitative Analysis of Medicinal Preparations."

After separating the medicinal components from the plaster base the character of the latter usually reveals itself more or less accurately by conducting the routine resin analysis. The values obtained can then be compared with the data recorded in the preceding pages.

Part IV

ORGANIC SUBSTANCES OTHER THAN ALKALOIDS AND GLUCOSIDES

CHAPTER XV

HYDROCARBONS—ALCOHOLS—ETHERS

A Classification of a group of substances under the term "synthetic" without reference to their chemical relationship is not feasible, and the limitations of the term " synthetic " are not easy to define. Certain substances are undoubtedly " synthetic " in all respects and, might easily be considered under such a heading; thus we have acetanilid, acetphenetidin, sulphomethan and saccharin, which, while they belong to definite groups of substances constitutionally, might be treated under one group from the standpoint of the analyst of medicinal products. On the other hand we have acetyl morphin, diacetylmorphin, eucain, anesthesin, euquinin, and homatropin, which are all products of the laboratory and yet are best treated under other headings, the morphin derivatives conjointly with the opium basis, the anesthetics with cocain, quinin derivations with quinin, and homatropin with its parent substance atropin. Again we meet with iodoform, dithymoldiiodide, bismuthbetanaphtholate and mercurol, which fall more naturally under the general consideration of iodine, bismuth, and mercury derivatives. It was therefore decided at the outset to arrange the material as nearly as possible according to its chemical relation, though deviations from this procedure must necessarily occur.

There have been a vast number of " new remedies " or " synthetics " evolved during the last two decades, but fortunately for the drug analyst the substances which are used in mixture are comparatively few and in most cases their separation and detection is not difficult. By far the greater number of these substances are dispensed by themselves either in their pure condition in prescriptions, or in pills, tablets, and capsules,

with some simple diluent or excipient. Their melting-points and general properties have been carefully determined, and after a few tests to determine their character, they may be assigned to their proper class and identified in this connection. The writer wishes to call especial attention to Professor Mullikin's work, "The Identification of Organic Substances," which will furnish valuable aid in pointing to the identity of an individual.

The substances of this group which have an extended use in medicine include acetanilid, acetphenetidin, antipyrin, chloroform, sulphomethane, sulphonethylmethane, phenolphthalein, saccharin, hexamethylenamin, chloral, acetyl salicylic acid, oxyquinolin, methylene blue, guaiacol carbonate, salol, salophen, resorcinol, and perhaps a few others. In the general scheme of drug analysis which is outlined in my work "Qualitative Analysis of Medicinal Preparations," the fractions in which these products will be found are indicated, and in the accompanying work there is given a detailed description of their properties and tests and an arrangement of the substances as nearly as feasible according to their chemical constitution.

Many of the substances described in this section are not themselves drugs, or medicinal agents, but as they may result from decomposition of other products which are drugs, and as their identification or determination may be important factors in the particular research under consideration, it is important that they should be discussed, and sufficient data assembled to aid the worker, without the necessity of consulting other works on organic chemistry.

HYDROCARBONS

The aliphatic hydrocarbons are of little moment to the drug chemist. The gaseous members of the methane, ethylene, and acetylene groups may be passed over unnoticed. The liquid and solid hydrocarbons of the methane group occur in petrolatum and paraffin

The saturated hydrocarbons of the aliphatic series are markedly indifferent substances. They are unaffected by acids or alkalies, are permanent in the air and sunlight, insoluble in water and but sparingly so in alcohol, though they go into solution with ease in ether and chloroform. Derivations of place of some of the lower members are used medicinally, but none of them can be prepared directly from the hydrocarbons themselves.

The hydrocarbons of the methane series have an important place in medicinal chemistry in the form of petrolatum or vaseline and in liquid petrolatum, white neutral oil, and albolene.

Petrolatum or vaseline varies in color from white to dark red, but the pharmacopoeial product cannot be darker than light amber. It is a soft,

unctuous mass, practically odorless and tasteless, but giving a faint petroleum-like odor on heating. It may be slightly fluorescent and is transparent in thin layers. Petrolatum melts 45°–50°, and is lighter than water. When heated to 60° its specific gravity is .820–.850. It is insoluble in water, but will emulsify with it if the mixture is stirred sufficiently. It is but slightly soluble in 95 per cent alcohol, but dissolves in boiling absolute alcohol and in ether, chloroform, petroleum ether, benzol, carbon disulphide, oil of turpentine, fixed and volatile oils.

Petrolatum is unsaponifiable and has no iodin value if pure. It resists the action of 85 per cent sulphuric acid, and is in general a very indifferent substance.

Liquid petrolatum may be water white to slightly yellowish with a bluish fluorescence. Its specific gravity is from .870–.940 at 25° C. and in all other respects its properties are the same as those of the solid form.

Petrolatum is the base of a great variety of ointments, cold creams, and petroleum emulsions. The liquid form has acquired considerable reputation in bowel troubles.

Paraffin which is a mixture of hydrocarbons of still higher melting-points, is a white, translucent substance of wax-like consistency. It is used to a large extent in ointments, pastes, and creams, acting as an agent to give the product its proper consistency.

Mixtures of petrolatum and ammonium oleate are marketed under proprietary names and are combined with iodin, sulphur, ichthyol, etc.

The determination of hydrocarbons in pharmaceutical mixtures and toilet preparations resolves itself practically into a measure of the unsaponifiable matter. The most satisfactory procedure for accomplishing this is one which was worked out in my laboratory by T. M. Rector, and the details follow:

Weigh from 5 to 10 grams of the oil or fat into a 300-mil Erlenmeyer flask, add 100 mils of alcoholic potash (40 grams per liter) and heat on the water-bath until saponification is complete. A small funnel in the neck of the flask will serve as a reflux condenser. After saponification, which usually takes from thirty to forty-five minutes, the hot soap solution is poured into a 16-oz. Squibb separator and the flask rinsed with two 25-mil portions of 95 per cent alcohol, making a total of 150 mils of 95 per cent alcohol. The separator is cooled to room temperature by shaking under the tap and 75 mils of light petroleum ether added. The petroleum ether dissolves in the alcohol, forming a clear solution.

About 125 mils of water are next added and the mixture shaken. At this point the petroleum ether will separate and rise to the surface of the alcohol-water mixture in a clear layer. The soap solution is drawn off into a second separator and extracted twice with 50-mil portions of petro-

leum ether. The combined petroleum ether extracts are filtered into a tared beaker and evaporated on the water-bath. The residue is dried in a vacuum desiccator and weighed.

To make a successful determination, the following points are essential:

1. Use a petroleum ether completely volatile under 80°.

2. The alcohol content of the soap solution after dilution with water should be very close to 55 per cent by volume. It is necessary to know the volume of the alcoholic potash solution as well as the amount of alcohol used in rinsing the flask. A lower content of alcohol than 50 per cent will result in emulsions, while a higher percentage than 60 will cause the retention of a large part of the petroleum ether in solution.

3. A beaker should be used for the final evaporation. The unsaponifiable matter will "creep" over the edges of an evaporating dish and cause low results.

4. The residue should be placed in a vacuum desiccator immediately after the petroleum ether has evaporated, to avoid loss by volatilization.

This method will of course give all of the unsaponifiable matter, including alcohols from waxes. These may be separated by boiling with acetic anhydride under a reflux and repeating the shaking-out process.

Some of the essential oils, notably oils of rose and chamomile, contain hydrocarbons in sufficient quantity to cause a solidification of the whole or a part of the sample. They are called stearoptenes, and are evidently mixtures of paraffins or olefines, the identity of which has not yet been ascertained. The stearoptene from rose oil melts 35°, and when distilled *in vacuo* separates into two fractions, melting 22° and 40–41° respectively.

Other essential oils in which hydrocarbons are known to occur include Arnica flower, dill, caraway herb, neroli, sassafras leaf, gaultheria, betula, and wild bergamot.

Benzol, C_6H_6

Benzol, benzene, phenyl-hydride or coal-tar naphtha is a colorless, mobile, highly refractive liquid, with a characteristic odor, specific gravity .883–.885 at 15°, boiling 80–81°, soluble in alcohol, ether, chloroform, glacial acetic acid, acetone and oils and insoluble in water. Below +6° C. it is a crystalline solid. Concentrated nitric acid at ordinary temperature converts benzol into nitrobenzol, $C_6H_5NO_2$, a substance with a characteristic odor, boiling 205°, known as "Oil of Myrbane." Sulphuric acid converts benzol into benzene-sulphuric acid, $C_6H_5SO_3H$. Chlorin and bromin act on benzol at moderately high temperatures or in presence of direct sunlight to form hexa addition compounds, $C_6H_6X_6$. At ordinary temperature or in the absence of sunlight substitution products are formed, $C_6H_5X_n$.

In medicine benzene is used as an antispasmodic in whooping cough and influenza. It is dispensed in capsule form, as an emulsion, and mixed with sugar.

Cymene. Methylisopropyl Benzene, $C_6H_4(CH_3)(C_3H_7)$

Cymene is capable of existing in three modifications, but the para form is the only one of interest to the drug chemist. It occurs in oil of thyme, and has been reported in the analysis of oils of Monarda punctata, Cuminum cyminum, Cicuta virosa and Origanum.

Para-cymene is a colorless liquid boiling 175–176° C., inactive to polarized light, with an agreeable odor resembling oil of lemons. Its specific gravity is .86 at 15°. Chromic acid or dilute nitric acid eventually convert it to terephthalic acid, which serves as a means for its identification. To carry out this reaction it is boiled under a reflux for thirty hours with excess of strong chromic acid mixture, or until the mixture dropping from the condenser is no longer oily. After cooling and diluting with water, the insoluble terephthalic acid is filtered off and purified by solution in ammonia, boiling with animal charcoal and reprecipitation by hydrochloric acid. The purified acid sublimes without melting.

Cymene may be identified by converting it to oxyisopropyl benzoic acid. It is treated with potassium permanganate in the proportion of 1–6 in a 4 per cent aqueous solution and boiled under a reflux. When the oxidation is complete, it is filtered, the filtrate evaporated, the potassium salt extracted with alcohol, the solvent evaporated, and an aqueous solution precipitated with dilute sulphuric acid, the filtered acid being recrystallized from alcohol. Melting-point, 155–156°.

Cinnamene or Styrene, $(C_6H_5CH=CH_2)$

Styrene is an unsaturated hydrocarbon having the composition of a phenylethylene. It occurs in liquid storax and is a colorless, highly refractive liquid, boiling 144–145° C., with a pleasant odor. It polymerizes readily to meta-styrene.

THE CYCLIC HYDROCARBONS

The cyclic hydrocarbons are of considerable interest to us owing to their prevalence in essential oils, many of which are used to a greater or less extent in drug products, and whose identity may sometimes be a question of importance.

These hydrocarbons may be considered as polymers of pentine, C_5H_6, and have been arranged by Wallach in the following classes:

A. Pentines or hemiterpenes, C_5H_8, as isoprene and valerylene.

B. Dipentines or terpenes, $(C_5H_8)_2$ or $C_{10}H_{16}$, including pinene, limonene, fenchene, camphene, phellandrene, etc.

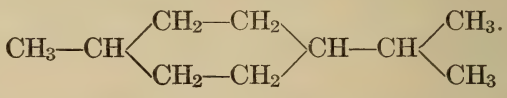
C. Tripentines or sesquiterpenes, $C_{15}H_{24}$, as cedrene and cubebene.

D. Diterpenes, $C_{20}H_{32}$, as colophene and copaivine.

E. Polyterpenes, $(C_5H_8)_n$, as the polyprene of caoutchouc.

Those of the *B* and *C* classes are of importance in this work. The chemistry of the diterpenes and polyterpenes is still in need of much extended research.

The terpenes are isomerides of the moleculer formula $C_{10}H_{16}$. They may nearly all be derived from a hydrocarbon terpane or menthane, $C_{10}H_{20}$, which has the composition of a methyl isopropyl cyclohexane.



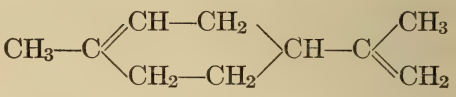
which is closely related to cymene and from which it may be derived by reducing the aromatic nucleus. It is convertible to cymene by oxidation.

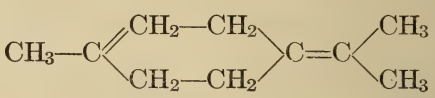
The terpenes, $C_{10}H_{16}$, which are the intermediate between cymene, $C_{10}H_{14}$, and terpane, $C_{10}H_{20}$, differ from the latter by four atoms of hydrogen in the molecule. They divide themselves into two groups containing in addition to the hexamethylene ring.

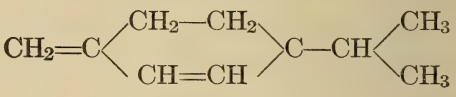
I. Two double bonds as in the monocyclic terpenes.

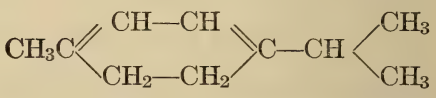
II. A double bond and a second ring system as in the dicylic terpenes.

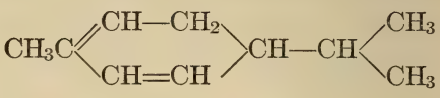
The structure of the monocylic terpenes is fairly well established.

Limonene and Dipentene 

Terpinolene 

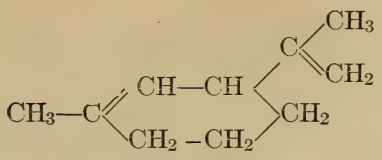
Beta-phellandrene 

[1] Terpinene 

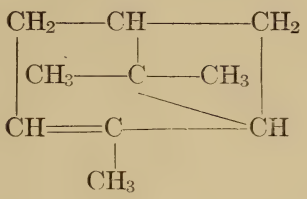
[1] Alpha-phellandrene 

[1] In these two both double bonds are in the nucleus, and they may be described as dihydro-*p*-cymenes.

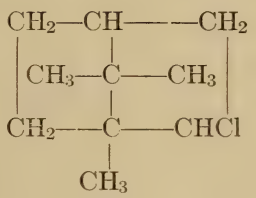
[1] Sylvestrene



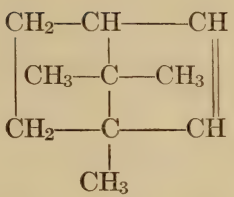
The structural formulas of the dicyclic terpenes is less clearly established. Pinene is probably



and its hydrochloride is



Bornylene is probably



The monocylic terpenes are characterized by generally forming tetrabromides, while the dicyclic terpenes usually form only dibromides, though they often add on 2HBr owing to the rupture of the ring systems by the acids.

With the exception of camphene, which is a solid, the terpenes are light, colorless, volatile, odorous liquids. They resemble each other closely in their physical properties, and are difficult to identify by resorting to these characteristics, and this is further complicated by the ease with which one terpene will change into another or from one modification to another.

By resorting to chemical means, better results will be obtained, and

[1] A meta-compound analogous to Limonene or Dipentene.

the formation of one or more of the following compounds will often serve to identify the terpene under investigation.

The bromides may be formed by dissolving 1 volume of the terpene in 4 volumes of alcohol and 4 of ether. The solution is well cooled by ice and .7 volume of bromin is slowly added. The crystalline precipitate is washed with cold alcohol and recrystallized from ether.

The nitrosochlorides may be prepared by dissolving the terpene in about $2\frac{1}{2}$ times its volume of glacial acetic acid, cooling in a mixture of ice and salt and adding the same quantity of ethyl or amyl nitrite. This mixture, after thorough cooling, is slowly treated with half its volume of a mixture of equal volumes of glacial acetic and concentrated hydrochloric acids, allowing time for the blue color to disappear before adding more acid. After fifteen minutes the crystals are filtered, washed with alcohol, dried at room temperature, dissolved in the least possible quantity of chloroform, from which solvent the nitrosochloride is reprecipitated by adding methyl alcohol. After drying its melting-point and microscopic appearance may be determined.

The nitrosobromides may be formed in the same way.

On treating the terpene nitrosochlorides with alcoholic potash or cautiously heating them alone, the elements of hydrochloric acid are removed and products of the composition $C_{10}H_{15}NO$ obtained.

The mono-hydrochlorides are formed by passing a stream of dry hydrogen chloride through the dry terpene.

The dihydrochlorides are produced by the action of moist hydrogen chloride. They are conveniently prepared by mixing a solution of the terpene in glacial acetic acid with glacial acetic acid saturated with hydrogen chloride. The dihydrochloride may be crystallized out of a mixture of alcohol and ether.

The dihydrobromides may be prepared in the same way.

The tetrabromides are prepared by dissolving the terpene in glacial acetic acid and adding bromide. The tetrabromide is recrystallized from ethyl acetate.

Sesquiterpenes, $C_{15}H_{24}$

The sesquiterpenes are viscous substances with higher specific gravity and boiling-points than the terpenes. When treated with bromin or iodine and the product distilled with water, cymene is produced.

Many sesquiterpenes have been described, but the individuality of all but a few is questionable. Caryophyllene is well established as the sesquiterpene of oil of cloves and it also occurs in copaiba.

The sesquiterpenes are characterized by the formation of dihydrochlorides and tetrabromides; nitrosochlorides (NOCl), nitrosates (N_2O_4) and nitrosites (N_2O_3).

TERPENES

Individual.	Pinene.	Camphene.	Fenchene.	Limonene.	Dipentene or *d-l*-limonene.	Sylvestrene.	Terpinolene.	Terpinene.	Phellandrene.
Source	Terpentine, Pine-needles, P. sylvestris, P. cimbia. Small quantity in many other oils	Isomerization of Pinene and reduction of camphor and borneol	Reduction of Fenchone from Fennel oil	Neroli, Caraway Orange-peel, Lemon, Dill, Lime, Fennel, Bergamot, Mandarin, Limette Erigeron, Celery, other oils	Isomerization of other terpenes. Occurs in Elemi, Turpentine, other oils	Russian and Swedish Turpentine oils	Isomerization of other terpenes	Isomerization of other terpenes	Fennel oils, Eucalyptus, amagdalina, Pinus montana, Star-anise, other oils
Specific Gravity	.858–.860 at 20°	.8422 at 54°	.864 at 20°	.846 at 20°	.845 at 20°	.848 at 20°		.847 at 20°	.8558 at 10°
Specific Rotation, $(a)_D$	±43°	±80.6°	0	+105° −107°	0	+66.3°	0	0	±17.6°
Ref-Index $(n)_D$	1.4566 at 21°		1.4690 at 20°	1.4731 at 20°	1.4731 at 20°	1.4757 at 20°		1.4846 at 20°	
Boiling-point	156°	m. 51–52° b. 158.5–159.5	160°	176°	178°	176°	185°	180°	170–172°
Monohydrochloride	Crystalline m. 125°	Crystalline 152°	Liquid	Liquid	Liquid	Liquid			
Dihydrochloride	m. 50°			50°	50°	72°	50°		
Dibromide	m. 169°	90°	Liquid				69	Liquid	
Tetrabromide			Liquid	104°	125–6°	135°	116°	Liquid	
Nitrosochloride	m. 103	No compound		100–107	103–104	106			
Nitrous deriv	$C_{10}H_{16}NO$ m. 132°			$C_{10}H_{14}NOH$ 72°	$C_{10}H_{14}NOH$ 93°			$C_{10}H_{16}N_2O_3$ 155°	$C_{10}H_{16}N_2O_3$ 103–104°
Nitrosate									
Nitrosite									

SESQUITERPENES

Individual.	Cadinene.	Caryophyllene.	Clovene.	Cedrene.	Humulene.	Patchoulene.	Zingiberene.	Cannibene.
Source	Cade, Pinus montana, P. sylvestris, Savin, Elderberry, Cedar wood, Cubeb, etc.	Cloves, Copaiba, Canella alba	Isomerization of Caryophyllene	Cedar wood	Hops	From patchouli camphor and $KHSO_4$	Ginger	Oil of Indian Hemp
Specific Gravity	.918 at 20°	.908 at 15°	.930 at 18°	.936 at 15°	.900 at 20°	.939 at 23°	.872 at 15°	.897 at 15°
Specific Rotation, $(a)_D$	−98.6°	−9°	−35.39°	−60°	+10.8°		−69−73.5°	−8.6°
Ref-Index $(n)_D$		1.50094	1.50066			1.50094	1.49399	
Boiling-point	272–275°	258–260°	261–263°	262–263°	263–266°	254–256°	269–270°	258–259°
Monohydrochloride								
Dihydrochloride	117–118°	69–70°			Liquid		168–169°	
Dibromide								
Tetrabromide							Liquid	
Nitrosochloride	93–94°	158°			164–167°		96–97°	
Nitrous deriv								
Nitrosate	105–110°	147–150°			162–162°		86–88°	
Nitrosite		α 113–114° β 146–148°			α 127° β 172°			

Terebene

Terebene is a pharmacopœial product consisting of dipentene and other hydrocarbons, obtained by the action of sulphuric acid on oil of turpentine and subsequent rectification with steam. It is a colorless limpid liquid, boiling 160–170° C., having an agreeable thyme-like odor. Its specific gravity is .860–.865 at 25° C., and it is only slightly soluble in water, but dissolves readily in alcohol, ether, carbonbisulphide, and glacial acetic acid. It is inactive to polarized light and thereby differs markedly from oil of turpentine. On exposure to light and air it becomes resinified and acquires an acid reaction.

It is used in a variety of ailments, including chronic bronchitis, flatulency, uterine cancer, genito-urinary diseases, and tubercular troubles.

Naphthalene, $C_{10}H_8$

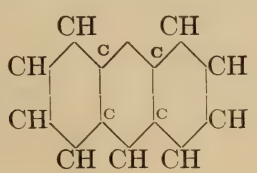
Naphthalene or tar camphor is a white scaly or crystalline substance, with a characteristic coal-tar odor, melting 79–80°, boiling 218°, insoluble in water, but to which it imparts its odor and taste on boiling, soluble in alcohol, ether, chloroform, fixed and volatile oils. Its vapor is inflammable, burning with a luminous, smoky flame, and it is volatile slowly at the ordinary temperature.

It yields a nitro-derivative and a sulphonic acid in a similar manner to benzol, and on boiling with dilute nitric or chromic acid is slowly oxidized, yielding carbon dioxide and orthophthalic acid. When dissolved in alcohol and treated with an alcoholic solution of picric acid, yellow crystalline naphthalene picrate, $C_{11}H_6 \cdot C_6H_2(NO_2)_3OH$, melting 149°, is formed.

Naphthalene possesses a number of therapeutic properties, but it has a limited use as a medicament. It has been employed in intestinal catarrh and inflammation, tapeworm, cholera, typhoid, and chronic bronchitis. Externally it may be encountered in ointments for skin diseases.

Anthracene, $C_{14}H_{10}$

Anthracene, with structural formula



crystallizes in colorless, lustrous plates, with blue fluorescence, melting 213°, boiling 360°. It is freely soluble in hot benzol, but only slightly in alcohol and ether. A saturated alcoholic solution mixed with an alcoholic solution of picric acid gives a precipitate of ruby-red needles of anthracene picrate, melting 138°. This compound may be resolved into its components when treated with considerable alcohol.

Anthracene itself has no interest to the drug chemist, but it is the basic substance of an important series of principles which are the active medicinal agents of the laxative drugs Cascara sagrada, Senna, Rhubarb, Rhamnus fragula, and Aloes. These principles are hydroxyanthraquinones.

Anthraquinone, $C_6H_4\begin{<}\begin{matrix}CO\\CO\end{matrix}\end{>}C_6H_4$, is formed by oxidizing anthracene with chromic acid. It forms pale yellow needles, melting 277°, and sublimes at higher temperature in long sulphur yellow needles. It is very stable and is attacked only with difficulty by oxidizing agents, sulphuric, or nitric acids.

Anthraquinone forms sulphonic acids when heated with sulphuric anhydride.

When a trace of anthraquinone is mixed with dilute sodium hydroxide, a little zinc dust added and the mixture boiled, an intense red color is produced, but on shaking in contanct with air the solution is decolorized. Oxanthranol is formed, which dissolves in alkali to a red solution, but in contact with air it is oxidized to anthraquinone, which separates as a white flocculent precipitate.

Anthraquinone on treatment with powerful reducing agents is finally converted to anthranol, $C_6H_4\begin{<}\begin{matrix}C(OH)\\|\\CH\end{matrix}\end{>}C_6H_4$.

Dihydroxyanthranol or anthrarobin, $C_6H_4\begin{<}\begin{matrix}COH\\|\\CH\end{matrix}\end{>}CH_2\begin{<}\begin{matrix}OH\\OH\end{matrix}\end{>}$, is used as an antiseptic in skin diseases. It is soluble in weak alkalies and hot alcohol, slightly in ether and chloroform.

Alizarin

Alizarin is α-β-dihydroxyanthraquinone, $C_6H_4\begin{<}\begin{matrix}CO\\CO\end{matrix}\end{>}C_6H_2(OH)_2$. It is a dark-red substance, melting 282°, almost insoluble in water, moderately in alcohol and readily in alkaline liquids, forming reddish-violet solutions. When distilled with zinc dust it is reduced to anthracene and with acetic anhydride it forms a diacetate, melting 180°.

Alizarin yields insoluble lakes with metallic oxides, the ferric compound is violet black, the calcium blue, the tin and aluminum different shades of red.

A piece of calico will be colored yellow by a solution of alizarin, but not fast. But if one previously mordanted with aluminum salt be used, a fast red will be formed on the cloth, or with iron a dark purple. The mordanting often requires two operations, first the cloth is soaked or boiled in an acetate or sulphate bath of the metal, then immersed in a weak alkali (ammonia, sodium carbonate, or lime) and then dipped in the alizarin solution.

These facts will be of service to the analyst who is concerned with the testing of the oxyanthraquinone principles of the aforesaid drugs.

Purpurin

Purpurin is α-β-α'-trihydroxyanthraquinone. Its isomeride, anthrapurpurin, $C_6H_3(OH)\begin{matrix}CO\\CO\end{matrix}C_6H_2\begin{matrix}OH\alpha\\OH\beta\end{matrix}$ in the form of the diacetate, is known as Purgatol, a yellow, tasteless powder, soluble in alkalies, but insoluble in water or dilute acids. It is used as a purgative. Anthrapurpurin forms yellowish-red needles, melting 330° C.

THE ALCOHOLS

The monohydric alcohols may be regarded as derived from the paraffins by the substitution of the monovalent hydroxyl group OH for one atom of hydrogen.

Methyl alcohol CH_3OH derived from methane, CH_3H.

Ethyl alcohol C_2H_5OH derived from ethane, C_2H_5H.

The dihydric alcohols or glycols may be considered as dihydroxy derivatives of the paraffins, forming an homologous series of the general formula $C_nH_{2n}(OH)_2$, the simplest of which is ethylene glycol.

Ethylene glycol, $C_2H_4(OH)_2$, from ethane, $C_2H_4H_2$.

The trihydric and polyhydric alcohols stand in the same relation to the glycols as the latter to the monohydric alcohols.

Propenyl alcohol, or glycerol, $C_3H_5(OH)_3$ from propane, $C_3H_5H_3$.

Erithritol, $C_4H_6(OH)_4$, from $C_4H_6H_4$.

Mannitol, $C_6H_6(OH)_6$, from $C_6H_8H_6$.

The alcohols play an exceedingly important part in drug and medicinal chemistry both as remedial agents and vehicles. The monohydric alcohols are represented by methyl and ethyl alcohol, and the trihydric alcohols by glycerol. The glycols themselves are not of great importance, but certain of the oxidation products, lactic, oxalic, succinic, tartaric, and citric acids, are of great value.

There are three classes of alcohols—primary, secondary, and tertiary. The primary alcohols may be said to be derived from methyl alcohol by substituting for one of the three hydrogen atoms united to the carbon, a hydrocarbon radicle, RCH_2OH. The secondary alcohols may be considered methyl alcohol, in which two of the hydrogen atoms united to the carbon are replaced by two hydrocarbon radicles R_2CHOH, and similarly in the tertiary alcohols all three hydrogen atoms are replaced by hydrocarbon radicles, R_3COH.

General Properties of the Monohydric Alcohols.—The lower members are colorless, neutral liquids with a burning taste and characteristic odor, miscible with water in all proportions and with nearly all organic liquids. As the molecular weight increases they change to oily liquids immiscible with water, and finally to waxy and crystalline solids.

The boiling-points increase with the molecular weight in the case of the primary alcohols, but the progression is broken with the isomeric forms, for instance primary propyl alcohol boils at 97° and primary butyl alcohol 117°, while tertiary butyl alcohol boils 83°, the same as does the secondary isopropyl alcohol.

The chemical reactions of the monohydric alcohols are with few exceptions due to the presence of the hydroxyl group, in many reactions they conduct themselves as alkyl substitution products of water, and in others they are analogous to metallic hydroxides. With sodium and potassium, hydrogen is evolved, but the resulting product is not a stable salt, being decomposed by water.

They produce ethereal salts with acids, yield halogen derivatives with phosphorus haloids, and are converted into olefines by dehydrating agents. On oxidation primary alcohols are converted to aldehydes and then into fatty acids, and secondary alcohols to ketones, both yielding oxidation products with the same number of carbon atoms as the original alcohol. Tertiary alcohols are decomposed, giving simpler acids or ketones.

Methyl Alcohol

Methyl alcohol has only a limited use in medicinal preparations. It is employed as the vehicle in some liniments and "balsams," and has occasionally been found in liquids intended for internal administration. Small quantities will sometimes be found in presence of a much greater proportion of ethyl alcohol, indicating that denatured alcohol has entered into the composition of the product under investigation.

Ordinary wood alcohol contains varying amounts of acetone and other volatile constituents occurring in wood distillate, and has a rank, unpleasant odor. There are several grades of the purified product, and those of the greatest purity are water white in color, with a characteristic pleasant odor differing somewhat from that of ethyl alcohol. The pure product

has a specific gravity of .796 at 15° C., boils 65–66°, and is miscible in all proportions with water, ether, and alcohol. It is inflammable, burning with a pale, non-luminous flame, and its vapor forms an explosive mixture with air or oxygen. Sodium and potassium dissolve readily with the formation of methylates and evolution of hydrogen, these methylates are extremely deliquescent and are immediately decomposed by water with regeneration of methyl alcohol. Methyl alcohol gives methyl chloride when saturated with hydrogen chloride gas, or on treatment with the chlorides of phosphorus. It gives methyl hydrogen sulphate when warmed with concentrated sulphuric acid, and normal methyl oxalate with oxalic acid. On oxidation it is converted into formaldehyde, which latter is further oxidized to formic acid. It does not give the iodoform reaction when warmed with iodine and alkali.

High-grade methyl alcohol for commercial purposes should leave but a trace of residue on evaporation, give no iodoform reaction indicative of acetone, no color with sodium hydroxide solution, 1.3 sp. gr., and not discharge the color of N/10 permanganate.

The drug analyst will be frequently called upon to identify methyl alcohol, which is easily accomplished by converting a portion of it into formaldehyde and identifying the latter by some characteristic color reaction. There are many tests described and as many procedures for obtaining the reactions. No attempt will be made to enumerate or repeat them all.

To begin with, the alcohol under investigation must be obtained in a condition which is as nearly pure as possible. If it is part of the formula of a complex medicine it must be distilled from the mixture, and if the distillate contains volatile oils they must be removed by shaking out with petroleum ether in the presence of sodium chloride and at a moderate dilution, and the alcohol again distilled from the salt.

Probably the best known test is that obtained by subjecting the distillate to the oxidizing influence of a red-hot copper spiral, and subsequently noting the appearance of a brilliant crimson color on adding sulphuric acid containing resorcinol.

Another good method depends on the formation of formaldehyde by the action of permanganate, the distillation of the aldehyde, and its identification by morphin dissolved in sulphuric acid. This procedure is really a combination of a method described by Henkel and one by Denigès.

The resorcinol test is carried out as follows:

Oxidize 10 mils of the liquid in a test-tube as follows: Wind copper wire 1 mm. thick upon a rod or pencil 7 to 8 mm. thick, in such a manner as to inclose the fixed end of the wire, and to form a close coil 3 to 3.5 cm.long. Twist the two ends of the wire into a stem 20 cm. long, and bend the stem at right angles about 6 cm. from the free end, or so that the coil may be

plunged to the bottom of the test-tube, preferably about 16 mm. wide and about 16 cm. long. Heat the coil in the upper or oxidizing flame of a Bunsen burner to a red heat throughout. Plunge the heated coil to the bottom of the test-tube containing the diluted alcohol. Withdraw the coil after a second's time and dip it in water. Repeat the operation from three to five times, or until the film of copper oxide ceases to be reduced. Cool the liquid in the test-tube meanwhile by immersion in cold water. Denigès[1] oxidizes the methyl alcohol to formaldehyde by the use of permanganate and then demonstrates the presence of the latter by fuchsin bisulphite. One mil of the alcohol to be examined is mixed with 5 mils of potassium permanganate 5 per cent and .2-mil sulphuric acid and after two to three minutes 1 mil of oxalic acid 8 per cent is added, shaken, and allowed to stand until the mixture assumes a yellow tint, then 1 mil, sulphuric acid is added. When the solution is completely decolorized 5 mils of fuchsin bisulphite solution is introduced and well mixed. After about fifteen minutes the violet color appearing in the presence of methyl alcohol reaches its maximum intensity. It is claimed that ethyl alcohol increases the efficiency of the test. With dilute solutions of methyl alcohol 3 mils are mixed with .1 mil ethyl alcohol and 2 mils permanganate 2.5 per cent, and the rest of the procedure conducted as outlined above.

Hinkel's method [2] was credited the most sensitive by Engelhardt and Jones, who made a comparative study of all the methods, and is as follows: One mil of the sample is placed in a small round-bottomed distilling flask and the oxidizing agent added; if ammonium persulphate is used .8 gram of the salt is added followed by 3 mils dilute sulphuric acid (1–5), or in the case of bichromate 1.5 gram of the salt and 1.5 mil sulphuric acid. In either case the mixture is diluted with water to 20 mils and then distilled, the distillate being collected in test-tubes in five separate portions of 2 mils each. The first two portions may be rejected. To each of the remaining portions a few drops of .5 per cent solution of morphin are added and concentrated sulphuric acid is introduced by means of a pipette so as to form a layer at the bottom of the tube. In the presence of formaldehyde a violet ring will be found at the junction of the two liquids.

The Riche and Hardy procedure for detecting and estimating methyl alcohol is also recommended if carried out according to the following directions:

The spirituous mixture is distilled, treated with potash, and rectified if necessary, to remove an undue amount of water.

Fifteen grams of coarsely powdered iodin are placed in a small Wurtz flask (about 60-mil capacity) connected with a Liebig condenser, and a quantity of the distilled spirit equivalent to 10 mils of strength of 60 per cent is added. The mixture is well shaken and then 2 grams of red phos-

[1] Compt rend., 150, 529 and 832. [2] Analyst, 1908, 33, 417.

phorus are added. The flask is shaken, connected immediately, allowed to stand ten to fifteen minutes with the condenser reversed, placed in a beaker or small water-bath which is gradually heated to 100° C.

The condensed alkyl iodides are collected under water in a graduated tube by means of a small adapter attached to the condenser. From 7 to 9 mils are usually obtained. After the whole of the iodides appear to have distilled over, a drop or two of potash solution is added to the water in the receiving tube, the whole shaken till colorless, transferred to a separator, washed, and finally run into a small flask containing a little dry K_2CO_3. After drying, the iodides are run into a small Wurtz flask attached to a short condenser, and having a thermometer in the neck, with the bulb opposite the exit tube. The flask is placed on a water-bath, which is slowly heated. If the spirit was free from methyl alcohol, the iodide will boil about 72° C. and steadily distill at that temperature. In the presence of the methyl compound, the initial boiling-point will be lower, and a proportion of the iodides will distill under 70° C.

The iodides are collected in a dry tube, and the first $2\frac{1}{2}$ mils are poured into a dry flask (75 mils capacity), $2\frac{1}{2}$ mils of aniline are added, the mixture shaken and gently warmed till it begins to crystallize. It is then set aside for twelve hours till the crystallization is complete.

To the crystalline mass about 50 mils of boiling water are added, and the mixture is kept boiling with constant shaking till perfectly clear. It is then cooled, a sufficient quantity of strong potash solution added to liberate the ethyl methyl aniline oil. By the addition of water it is thrown up into the neck of the flask, removed with a pipette, and the flask washed and nearly filled with pure water into which the oil is returned, well shaken, and thrown up into the neck as before.

One mil of this oil is then intimately mixed with 10 grams of the following oxidizing mixture placed on a wide test-tube, closed with cotton wool and heated for ten or twelve hours at a temperature of 90° C.

Dry quartz sand	100 grams
Nitrate of copper	3 grams
Chloride of sodium	2 grams

After oxidation the mixture is extracted four times with about 20 mils of warm alcohol, filtered into a 100-mil flask, and made up to the mark at 15° C. Five mils of alcoholic extract are made up to 100 mils with distilled water, and after shaking, 2 mils of this is mixed with 400 mils of water in a large beaker.

Into this 3 feet of white Berlin wool previously boiled in water rendered just alkaline, and then well washed in pure water, are placed, and the whole warmed to keep it at a temperature not exceeding 75° C. till all the color is extracted. The wool should be stirred round occasionally with a glass rod.

The wool after washing and drying will have only a pale reddish-violet tint if the alcohol was pure. If methyl alcohol was present the violet is much more intense, increasing in depth according to the percentage present in the mixture.

An approximate estimation of the percentage can be made by comparing the dye given with that from known mixtures treated in the same way.

In the presence of small quantities of methylated spirit the dyes may be somewhat doubtful. In such cases it is necessary to transform a larger quantity (30–50 mils) of the purified alcohol into the iodides, and then carefully to fractionate the latter by means of a small column of glass beads. Each of the first three or four fractions is separately oxidized, The methyl compound is largely accumulated in first and second fractions. which give a more intense dye than the latter fractions.

With pure ethyl alcohol there is no appreciable difference in the dyes from different fractions.

Essential oils, camphor, etc., occurring in pharmaceutical preparations should be separated from the spirit before preparing the iodides. In the case of ether etc., the spirit present would have to be washed out and concentrated.

Vorisek,[1] in an interesting review on the work done in the matter of detecting methyl alcohol, has described a method which is valuable on account of its rapidity and because but a very small quantity of material is necessary.

The solutions required include:

Chromic Acid Solution.—.8 per cent CrO_3 free of H_2SO_4.

Albumen Solutions.—Aldehyde-free milk or the white of one fresh egg mixed with 50 mils of clear water filtered and preserved with a few drops of chloroform.

Ferric Chloride Solution.—.4 per cent.

Sulphuric Acid.—Free from nitric and nitrous acids.

Five-tenths to one mil of the sample of alcohol is placed in a 6-inch test-tube, 1 mil of the chromic acid solution added, and the liquid diluted with water to 4 or 5 mils. Small pieces of pumice are dropped in, the test-tube connected with a long air condenser and the liquid distilled into another tube by boiling briskly over a small flame. When only about .5 mil remains behind in the first test-tube, the condenser is detached and rinsed with about 2 mils of water into the receiving test-tube. To the distillate are added: 1 drop ferric chloride solution, 2 drops of albumen solution, and after mixing 4 to 5 mils of the pure sulphuric acid are poured in slowly and carefully as a layer, generation of much heat being avoided. The zone of the contact is then observed, without disturbing the liquids, against a white background. A sharply defined violet zone appears almost

[1] J. Soc. Chem. Ind., 1909, 28, 823.

at once if the portion of methyl alcohol is above 5 per cent. With smaller amounts but more than 1 per cent the color shows within one minute. Several minutes will be required for the color to appear with less than 1 per cent of methyl alcohol. Pure ethyl alcohol treated in this manner gives no color. When organic impurities are present which cannot be removed a yellow to reddish color is often obtained, but not violet.

Albumen in strong solutions gives with concentrated sulphuric acid a variety of color reaction. It must not be used in excess and only traces of ferric chloride should be added to obtain perfect blank tests.

Under the conditions here described it was possible to detect as little as .001 gram of methyl alcohol in 1 mil of the ethyl compound.

For determining methyl alcohol, the procedure to be employed for obtaining a distillate free from extraneous substances is the same as given for ethyl alcohol in the general methods, page 2. The distillate obtained in this way may still contain acetone, from which it may be freed by conversion into iodoform and the latter removed by shaking out with petroleum ether or chloroform, the solvent being washed with saturated salt solution and the washings added to the main liquid. The liquid is then distilled and the distillate made up to definite volume, and the methyl alcohol estimated from the refractive index and the specific gravity according to the tables.

Doroszewski and Devorzanczyk [1] state that the values previously given in the literature for the refractive index of anhydrous methyl alcohol are incorrect. The authors determined the values for pure methyl alcohol and its mixtures with water, using the Zeiss immersion refractometer and compiled the following table:

REFRACTIVE INDICES OF MIXTURES OF METHYL ALCOHOL AND WATER

Per Cent of Alcohol by Weight	15 n_D	17.5 n_D	Per Cent of Alcohol by Weight	15 n_D	17.5 n_D
100	1.33057	1.32957	40.00	1.34308	1.34248
95.00	1.33309	1.33212	35.02	1.34235	1.34180
90.01	1.33545	1.33450	30.02	1.34138	1.34091
85.01	1.33749	1.33657	24.98	1.34022	1.33980
80.00	1.33925	1.33835	20.00	1.33879	1.33844
75.01	1.34067	1.33980	15.01	1.33730	1.33702
69.99	1.34179	1.34094	12.00	1.33644	1.33616
64.99	1.34272	1.34192	10.04	1.33584	1.33559
60.03	1.34327	1.34250	7.04	1.33504	1.33480.
54.99	1.34365	1.34290	5.00	1.33453	1.33429
49.98	1.34378	1.34308	2.00	1.33384	1.33362
45.03	1.34359	1.34294	0	1.33339	1.33320

[1] J. Russ Phys. Chem. Ges., 1099, 41, 951; J. S. C. I., 1910, 29, 373.

TABLE GIVING THE SPECIFIC GRAVITIES OF AQUEOUS METHYL ALCOHOL AT 0° AND 15.56° C. WATER AT 4° = 1000.

Per Cent by Weight of CH_3OH	Specific Gravity at 0°	Specific Gravity at 15.56°	Per Cent by Weight of CH_3OH	Specific Gravity at 0°	Specific Gravity at 15.56°	Per Cent by Weight of H_3COH	Specific Gravity at 0°	Specific Gravity at 15.56°
0	999.87	999.07	35	953.54	945.67	70	886.87	874.87
1	998.06	997.29	36	952.04	943.99	71	884.70	872.62
2	996.31	995.54	37	950.51	942.28	72	882.37	870.21
3	994.62	993.82	38	948.95	940.55	73	880.03	867.79
4	992.99	992.14	39	947.34	938.77	74	877.67	865.35
5	991.42	990.48	40	945.71	936.97	75	875.30	862.90
6	989.90	988.93	41	944.00	935.10	76	872.90	860.42
7	988.43	987.26	42	942.39	933.35	77	870.49	857.93
8	987.01	985.69	43	940.76	931.55	78	868.06	855.42
9	985.63	984.14	44	939.11	929.75	79	865.61	852.90
10	984.29	982.62	45	937.44	927.93	80	863.14	850.35
11	982.99	981.11	46	935.75	926.10	81	860.66	847.79
12	981.71	979.62	47	934.03	924.24	82	858.16	845.21
13	980.48	978.14	48	932.29	922.37	83	855.64	842.62
14	979.26	976.68	49	930.52	920.47	84	853.10	840.01
15	978.06	975.23	50	928.73	918.55	85	850.55	837.38
16	976.89	973.79	51	926.91	916.61	86	847.98	834.73
17	975.73	972.35	52	925.07	914.65	87	845.39	832.07
18	974.59	970.93	53	923.20	912.67	88	842.78	829.38
19	973.46	969.50	54	921.30	910.66	89	840.15	826.68
20	972.33	968.08	55	919.38	908.63	90	837.51	823.96
21	971.20	966.66	56	917.42	906.57	91	834.85	821.23
22	970.07	965.24	57	915.44	904.50	92	832.18	818.49
23	968.94	963.81	58	913.43	902.39	93	829.48	815.72
24	967.80	962.38	59	911.39	900.26	94	826.77	812.93
25	966.65	960.93	60	909.17	897.98	95	824.04	810.13
26	965.49	959.49	61	907.06	895.80	96	821.29	807.31
27	964.30	958.02	62	904.92	893.58	97	818.53	804.48
28	963.10	956.55	63	902.76	891.33	98	815.76	801.64
29	961.87	955.06	64	900.56	889.05	99	812.95	798.76
30	960.57	953.55	65	898.35	886.76	100	810.15	795.89
31	959.21	952.11	66	896.11	884.43			
32	957.83	950.53	67	893.84	882.02			
33	956.43	948.94	68	891.54	879.70			
34	955.00	947.32	69	889.22	877.14			

Ethyl Alcohol

Ethyl alcohol has such an extensive use in medicinal preparations that dilation on this point would be superfluous. As a drug pure and simple it is employed mainly by the practitioner in individual cases, and hence in general it functionates as a vehicle and solvent, and not as a drug. Nevertheless, under the Food and Drugs Act it falls in the class of inhibited articles that must be declared in exact terms on the label, and in the specific clause where it is mentioned there is no limitations as to its use whether it be as a remedy itself, or simply as a vehicle or solvent in the same class as water or glycerin.

The alcohol of commerce includes absolute alcohol, which contains not more than 1 per cent by weight of water. Cologne spirits, or U. S. P. Alcohol, 94.9 per cent by volume and 92.3 per cent by weight; alcohol 94 per cent by volume, used in large amounts for commercial purposes, dilute alcohol 48.9 per cent by volume and 41.5 per cent by weight, and denatured alcohol.

The grade of alcohol which has the greatest use is the 94 per cent product. In regulation 28 for the enforcement of the Food and Drugs Act, it states in paragraph (A) that " The term ' alcohol ' is defined to mean common or ethyl alcohol," and in regulation 30 that "the expression of 'quantity' or 'proportion' shall mean the average percentage by volume in the finished product." Now while it is well known to a chemist that the percentage of alcohol is always given in terms of absolute alcohol and that the statement " common or ethyl alcohol " refers to the chemical composition of the alcohol and not to the commercial grade, the term used in the regulation furnishes an excellent subject for legal quibbling where there is a conflict of testimony over the quantity of alcohol present in a mixture. This should be borne in mind by any analyst who is concerned in a case involving the question of alcoholic percentage, and be fully explained to the attorney before the evidence is introduced in order that the latter may be prepared for proper interrogatory.

Pure ethyl alcohol is a transparent, colorless, very limpid liquid, inflammable, of a pleasant spirituous odor and burning taste, has a specific gravity of .797 at 15.6°, boils about 78°, solidifies below –30°, and is miscible in all proportions with water, ether, and chloroform. It resembles methyl alcohol in chemical properties, forming ethylates with sodium and potassium, which are readily decomposed by water, combining with acids to form ethereal salts, and forming halogen compounds with phosphorus halides. On oxidation it is converted to acetaldehyde and acetic acid. It gives the iodoform reaction with iodin and alkali and this reaction is commonly used to demonstrate its presence, though many other substances, including acetone and acetaldehyde, will give the same test. The lactic acids

give it, and β-hydroxybutyric, quercitol, inositol, pyruvic acid, and aldol all give precipitates having a characteristic odor, though they may consist of homologues or substitued derivatives of iodoform.

The detection of ethyl alcohol can be accomplished in a distillate from the product under investigation. If there is reason to suspect the presece of ether, chloroform, volatile oil, or other material soluble in petroleum ether, the distillate must be diluted, saturated with sodium chloride, and shaken out two or three times with petroleum ether of low boiling-point. The solvent is washed with saturated sodium chloride solution, which is returned to the main liquid and the latter redistilled and the neutrality of the distillate assured.

The presence of ethyl alcohol may be established by the formation of ethyl acetate, when the sample is warmed with an acetate and sulphuric acid.

With iodin and an alkali acetone yields iodoform in the cold. With the same reagents alcohol yields iodoform at 70° C.

To 2 or 3 mils of the distillate add 2 or 3 drops of 1 per cent solution of sodium nitroprusside, and then 2 or 3 drops of 10 per cent solution of sodium hydroxide. Divide into 2 portions, *a* and *b*. To *b* add 3 to 5 drops of glacial acetic acid. In the presence of as much as 1 or 2 per cent of acetone *a* is at first orange or yellow-orange colored, changing after twenty minutes to a clear yellow; *b* is at first red when viewed against a white background, the hue being unchanged after twenty minutes, although the intensity decreases so that in the case of solutions containing as little as 1 per cent of acetone the color is so pale as to be barely distinguishable.

To 10 mils of the distillate add 1 gram solid KOH, and without waiting for this to dissolve add 10 drops salicylaldehyde and warm the whole at 70°. In the presence of acetone a purple-red contact ring develops; or, if the hydroxide is all dissolved before the addition of the salicylaldehyde, the liquid becomes yellow, then reddish, and finally purple-red.

Appreciable quantities of aldehyde will be detected by the odor, and small amounts by the pink color, which develops on adding fuchsin decolorized by sulphurous acid, though it may be here noted that almost any alcoholic distillate will give a test for aldehyde.

Methyl alcohol may be detected by the tests described under that substance.

The determination of ethyl alcohol in medicinal preparations has been described on page 2 under the general methods.

When the distillate contains both methyl and ethyl alcohol the percentages of each can be ascertained by the method and tables of Leach and Lythgoe. In using this method the worker should always assure himself by previous qualitative test that his distillate contains methyl alcohol, and that it is free from essential oils and other substances having refrac-

tive indices. Unless this is done he may be subjected to much embarrassment by reporting a percentage of methyl alcohol and finding out too late that none is present. The writer in checking over the work of other men has more than once saved an overzealous chemist the chagrin of having to refute his analysis in contest when he had erroneously reported a definite percentage of methyl alcohol without making a qualitative test.

Determine at 20° C. the refraction of the distillate obtained in the determination of alcohol by the immersion refractometer. If on reference to the table the refraction shows the percentage of alcohol agreeing with that obtained from the specific gravity, it may safely be assumed that no methyl alcohol is present. If, however, there is an appreciable amount of methyl alcohol the low refractometer reading will at once indicate the fact. If the absence from the solution of other refractive substances than water and the alcohols is assured, this qualitative test by difference in refraction is conclusive.

The addition of methyl alcohol decreases the refraction in direct proportion to the amount present; hence the quantitative calculation is readily made by interpolation in the table on page 540, using the figures for pure ethyl and methyl alcohol of the same alcoholic strength as the sample.

A rapid method for Determining Alcohol and Ether in Mixtures of both has been devised by Julius Fleisher and Heinrich Frank.[1]

This method depends on the fact that when a mixture of ether, alcohol and water is treated with benzin, two distinct layers are formed, the benzin taking up the ether while the volume increase of the water added gives the alcoholic content.

Ten mils of the mixture of alcohol and ether are mixed with 5 mils benzin and 5 mils water in a glass cylinder. After a few minutes a sharp separation takes place and two layers are formed. The increase in volume of benzin and water layers gives the proportion of alcohol and ether.

In a mixture of alcohol, ether, and water, the specific gravity of the three is first determined, then the volume of ether as above. With these data the alcohol can readily be determined by the following formula

$$S = \frac{10d - (a \times .729)}{10 - a},$$

where S = the sp. gr. of the alcohol and water;
d = the sp. gr. of the ether alcohol mixture;
a = number of mils ether; .729 sp. gr. of ether.

From S the alcohol can be calculated in the usual manner.

Example: Sp. gr. of mixture, .880.
Increase in benzin, 2 cm.

$$S = \frac{8.800 - (2 \times .729)}{10 - 2} = .917 = 58 \text{ per cent alcohol.}$$

[1] Apoth. Zeit. No. 55, 1907, page 579.

Scale readings of the Zeiss immersion refractometer at 20° C., corresponding to each per cent by weight of methyl and ethyl alcohols

Per Cent Alcohol by Weight	Scale Readings		Per Cent Alcohol by Weight	Scale Readings		Per Cent Alcohol by Weight	Scale Readings	
	Methyl Alcohol	Ethyl Alcohol		Methyl Alcohol	Ethyl Alcohol		Methyl Alcohol	Ethyl Alcohol
0	14.5	14.5	35	35.8	75.8	70	33.0	100.0
1	14.8	16.0	36	36.3	76.9	71	32.3	100.2
2	15.4	17.6	37	36.8	78.0	72	31.7	100.4
3	16.0	19.1	38	37.3	79.1	73	31.1	100.6
4	16.6	20.7	39	37.7	80.2	74	30.4	100.8
5	17.2	22.3	40	38.1	81.3	75	29.7	101.0
6	17.8	24.1	41	38.4	82.3	76	29.0	101.0
7	18.4	25.9	42	38.8	83.3	77	28.3	100.9
8	19.0	27.8	43	39.2	84.2	78	27.6	100.9
9	19.6	29.6	44	39.3	85.2	79	26.8	100.8
10	20.2	31.4	45	39.4	86.2	80	26.0	100.7
11	20.8	33.2	46	39.5	87.0	81	25.1	100.6
12	21.4	35.0	47	39.6	87.8	82	24.3	100.5
13	22.0	36.9	48	39.7	88.7	83	23.6	100.4
14	22.6	38.7	49	39.8	89.5	84	22.8	100.3
15	23.2	40.5	50	39.8	90.3	85	21.8	100.1
16	23.9	42.5	51	39.7	91.1	86	20.8	99.8
17	24.5	44.5	52	39.6	91.8	87	19.7	99.5
18	25.2	46.5	53	39.6	92.4	88	18.6	99.2
19	25.8	48.5	54	39.5	93.0	89	17.3	98.9
20	26.5	50.5	55	39.4	93.6	90	16.1	98.6
21	27.1	52.4	56	39.2	94.1	91	14.9	98.3
22	27.8	54.3	57	39.0	94.7	92	13.7	97.8
23	28.4	56.3	58	38.6	95.2	93	12.4	97.2
24	29.1	58.2	59	38.3	95.7	94	11.0	96.4
25	29.7	60.1	60	37.9	96.2	95	9.6	95.7
26	30.3	61.9	61	37.5	96.7	96	8.2	94.9
27	30.9	63.7	62	37.0	97.1	97	6.7	94.0
28	31.6	65.5	63	36.5	97.5	98	3.5	93.0
29	32.2	67.2	64	36.0	98.0	99	3.5	92.0
30	32.8	69.0	65	35.5	98.3	100	2.0	91.0
31	33.5	70.4	66	35.0	98.7			
32	34.1	71.7	67	34.5	99.1			
33	34.7	73.1	68	34.0	99.4			
34	35.2	74.4	69	33.5	99.7			

METHOD FOR ESTIMATING ALCOHOL IN THE PRESENCE OF CARBOLIC ACID

The following procedure is described by J. Erlich.[1]

Pipette 50 mils of sample into a 300-mil flask containing 30 mils water, made strongly alkaline with an excess of strong NaOH solution, so that the final volume is about 100 mils and the odor of phenol is absent. Add glass beads and distill into a 50-mil graduated flask containing 1 or 2 mils water. The end of the condenser or adapter should almost touch the surface of the distillate in the receiver, especially at the beginning of a distillation. A drawn-out thistle tube is serviceable in this connection. The flask is lowered as distillation proceeds.

When nearly 50 mils of distillate have been collected, remove the receiver, dilute with water to mark, shake thoroughly and pipette 25 mils into another 300-mil flask containing 30 mils water.

Precipitate the phenol as its tribromderivative by adding bromin water, drop by drop, to slight excess while rotating flask. Without delay add normal " hypo " solution (a few drops will be sufficient to decolorize; i.e., to remove the free bromin excess), and finally add enough strong NaOH solution to dissolve the white tribromphenol as its phenate, and then a decided excess of alkali. The final volume will be less than 100 mils. After the addition of glass beads distill into the 50-mil flask as before, dilute to mark and determine density by weighing. The percentage of alcohol in this last distillate multiplied by two gives the required figure.

For higher concentration of alcohol a 100-mil receiving flask may be substituted in the above method, and 50 mils of the distillate treated and redistilled. For high concentrations of phenol the method is directly applicable, since the amount of phenol which passes over during the first distillation is small. If the original phenol content is low, the first distillation may be omitted. In this case the 50-mil sample plus 30 mils water in the 300-mil flask is treated directly with the bromin water to slight excess as shown by color; then add " hypo," alkali, etc., as above and distill into 50 or 100-mil flask according to alcohol concentration. Samples high in phenol cannot be treated in this manner, because the bulky precipitate of tribromphenol prevents thorough mixing while adding the bromin water, making it impossible to perceive when an excess of bromin is present.

The hydrobromic acid formed by the action of bromin on the phenol is neutralized and retained by the alkali.

[1] J. Ind. and Eng. Chem., 1916, 8, 240.

PROPYL AND BUTYL ALCOHOLS

None of the isomers of those two alcohols by themselves are of any importance in medicinal chemistry. Propaesin, one of the newer anesthetics, which is the propyl ester of paramido-benzoic acid, would probably, under proper conditions of hydrolysis, yield propyl alcohol, and there are several ethereal salts with the propyl and butyl radicles which might occasionally require identification. Chloretone or acetone-chloroform is a place derivative of tertiary butyl alcohol, and has quite an extensive use as an anesthetic and hypnotic.

TRIHYDRIC AND POLYHYDRIC ALCOHOLS

Glycerol

The simplest trihydric alcohol is glycerol, $C_3H_5(OH)_3$. This substance has a wide use in the preparation of medicines, though as a drug itself its employment is limited. It occurs as a preservative, a vehicle, and a solvent in liquid preparations, and takes part in many external remedies as an emollient, as a lubricant in suppositories, and as a laxative. Commercial glycerin is a thick syrup containing about 95 per cent of pure glycerol, and is chiefly obtained from the residues in the manufacture of soap. Of late years the demand for a pure article has been so rigid and the improvements in manufacture so rapid, that it is a simple matter to obtain a product of the highest refinement.

Glycerin is a component of many liquid drug extracts which are used in the formulas of complex preparations, and its identification often serves indirectly to substantiate the presence of these drugs.

Pure glycerol is a colorless, crystalline substance, melting 17°, but it does not solidify readily, owing to the presence of water, which it absorbs with great avidity from the air up to 50 per cent. When pure it boils at 290° without decomposition. It mixes in all proportions with alcohol and water, but is slightly soluble in ether, and is insoluble in petroleum ether. It has a sweet taste. It loses weight gradually when heated at the temperature of the water-bath. When heated with dehydrating agents, potassium hydrogen sulphate, sulphuric acid, or phosphorus pentoxide, it is decomposed into acrolein and water, the former readily recognized by its disagreeable odor and irritating effect on the mucous membrane. On careful oxidation it yields glyceric acid, $CH_2OHCHOHCOOH$, but usually a mixture of oxalic, glycolic, and carbonic acids results. It forms mono-, di-, and tri-esters with acids, the derivatives obtained with hydrochloric acid are called chlorhydrins. The trinitrate, known as nitroglycerin, is a very important medicinal agent, and the glycerophosphates have an extensive use

The writer, with L. F. Kebler, had occasion to make a critical survey of the glycerin produced by all of the different manufacturers in this country and of the imported products.

The claim had often been advanced that the present glycerin standard is too rigid and in certain respects can rarely be attained; hence the Pharmacopœia should be so modified that it will be consistent with conditions which actually exist. To confirm or refute this statement it was necessary to investigate the quality of the glycerin on the market in the United States, and to determine exactly to what extent samples from different sources conform to the tests prescribed in the Pharmacopœia. Another purpose was to learn whether there were any glycerins which would not reduce Fehling's solution, the claim that no such article was obtainable being of importance owing to the use of glycerin in the preparation of Haines's solution, an alkaline copper liquid which has been recommended for detecting sugar in urine and whose value as a testing reagent would naturally be impared if reduction occurred when no sugar was present.

The samples were examined first according to the methods prescribed in the Pharmacopœia. A rigid examination was made for arsenic in order to determine whether even traces of this substance were left in the glycerin; special tests were made to note the action of Fehling's solution, and a sample of Haines's solution was made up with each product. The physical appearance was good in every instance. The samples were all neutral to litmus paper. The specific gravities at 25° C. varied from 1.248 to 1.258, in most cases being above 1.250, with an average of 1.254. In this respect they were all above the standard requirement of 1.246 at 25° C.

The pharmacopœial test for sugar gave negative results, as would be expected. Experiments were then conducted noting the action of Fehling's solution, using concentrated and diluted glycerin and without previously heating with acid as in performing the sugar test. Two samples which reduced Fehling's solution in the undiluted state gave no reduction on dilution; two reduced the solution on diluting, but did not in the concentrated condition; three showed no reduction either diluted or undiluted; while the remainder reduced Fehling's solution under any condition. Several of the samples which reduced Fehling's solution in the undiluted condition had reduced ammoniacal silver nitrate in the Hager test.[1] Haines's solution when made according to directions given in works on urinalysis [2] was reduced in every instance, thereby substantiating the claims which had already been advanced in this connection.[3]

[1] Handbuch der Pharm. Praxis, 4th ed., 1905, 1 : 1221.

[2] Purdy, R. G., Practical Urinalysis and Urinary Diagnosis, 1895, page 103.

[3] Mayer, J. L., The Reducing Action of Glycerin, Merck's Report, 1905, 14 : 165.

Most of the samples were well within the requirements as to the color imparted by concentrated sulphuric acid, various shades of yellow occurring. One sample was dark brown and fluorescent, while another turned brown and gave off a strong fatty odor. In fact, the odor varied more than the color, some samples having the fatty odor just mentioned, while others had an unmistakably pleasant aromatic smell; four had a characteristic hydrocarbon odor, and in one instance the product was practically without color or odor, but evolved a quantity of minute gas bubbles. When the samples were treated with alcohol and sulphuric acid and warmed on the steam-bath ethereal odors were noted in all cases, the unpleasant butyric ester predominating, although with two samples an agreeable fruity odor was noticed. In certain instances this test ran parallel with the former one, in that samples which gave scarcely any color or odor with sulphuric acid gave but a slight ethereal odor, but for the most part these tests were entirely at variance. When simply heated on the steam-bath marked differences in odor were noted, four samples gave off a slight odor of no particular character, two an aromatic odor, and the remainder a fatty odor of varying intensity.

A reaction was obtained showing a slight trace of sulphates in five products, a trace of chloride in two, and a reduction of silver nitrate in five, this being very marked with one specimen; oxalates were indicated in two samples from the same manufacturer; heavy metals were shown in three cases, while six gave no reactions for metals or acids.

Only one sample showed the presence of objectionable amounts of arsenic, and this was of foreign make and labeled "arsenic free." The Marsh test was rigidly applied to every glycerin in order to determine how completely the arsenic had been eliminated, six specimens gave no mirror, and the others, with the exception of the one above mentioned, contained less than one part in a million. It is of interest to note that of two samples submitted by one manufacturer one contained arsenic and the other did not.

Satisfactory results seemed impossible with the pharmacopœial test using ammoniacal silver nitrate; reduction took place in every instance, and it was apparent that no significant conclusions could be drawn from its use. Accordingly it was abandoned for the test described by Hager,[1] with which better comparative results were obtained. Five mils of the sample were mixed with 5 mils of 26 per cent ammonia water and 5 drops of silver nitrate added; the mixture was allowed to stand at the ordinary temperature in the dark for fifteen minutes and its appearance noted. There was no reduction of the silver nitrate in six cases, and a marked reduction in two, the other samples being slightly colored.

The investigation showed that glycerin could be produced which would

[1] Loc. cit.

answer all of the pharmacopœial requirements with the exception of the ammoniacal silver nitrate test. It also showed that although some glycerins gave off a fruity odor when treated with alcohol and sulphuric acid, they were otherwise of good quality; therefore the wording of this test should be modified in order to include the disagreeable butyric odor as it now discriminates only against a " Fruity odor."

It appeared from this investigation that a high-grade glycerin should meet the following requirements:

Its specific gravity should be about 1.250 at 25° C.

It should be neutral to litmus paper.

It should leave no ash on ignition.

It should give off but a slight odor when heated alone at the temperature of the water-bath.

It should not give off an unpleasant ethereal odor nor a strong fruity odor when warmed with alcohol and sulphuric acid.

It should not develop more than a yellow color when mixed with an equal volume of sulphuric acid and no disagreeable odor should be evolved.

When treated with silver nitrate and ammonium hydroxide, according to Hager, no color, or at most only a yellow color, should develop.

It should give no reaction for sulphates, chlorides, oxalates, or metals.

It should give no reaction for sugars.

When diluted with an equal volume of water it should give no reduction with Fehling's solution.

It should not contain arsenic in excess of the limit prescribed in the Pharmacopœia.

IDENTIFICATION OF GLYCERIN

The question of the detection and determination of glycerin in mixtures may or may not be of great importance in our work. Its detection is simple in any case and its accurate estimation is not of moment, except were the analyst desires to bring the percentage of a mixture up to 100. But it might as well be emphasized at this point that in our present state of knowledge, the accurate estimation of glycerin is difficult in complex mixtures of this kind. In the residues from soap stocks the glycerin may be determined by the " acetin " method, and in some medicinal mixtures it might be possible to arrive at the amount of glycerin by the same procedure after removing interfering substances. But usually the evaporations and precipitations cause such losses that any determination is of little value.

The presence of glycerin in a mixture is first apparent in running an ash determination, for as soon as a sufficient condensation has been reached and the mass has taken fire, little sky-rocket evolutions become apparent,

which fly off in parabolic curves, sometimes twisting like serpents and leaving trails of white smoke.

In the general scheme of the qualitative analysis outlined in my work on that subject, glycerin will remain in the aqueous solution through both the acid and alkaline shake-out, and then can be purified, and identified by the following reactions:

Mullikin's Reaction.—The residue suspected to be glycerin and which has been purified by the lime-alcohol ether treatment (see below) should be made up with water to a dilution of about 1 per cent. Add 5 drops 1 per cent solution pyrogallic acid, then 3 mils conc. sulphuric acid. Shake and heat to boiling and boil for about half a minute. If glycerin is present a purple color will begin to develop, deepening as the boiling is continued. Cool and add about 20 mils alcohol when the purple color shows to advantage.

Mandel and Neuberg have worked out a method for detecting glycerin by converting it to glycerose, which is then identified by the orcin reaction. About 2 mils of the glycerin solution are mixed with normal sodium hypochlorite solution and the mixture boiled for one minute. The addition of hypochlorite and boiling are repeated, the hot solution treated with three drops of hydrochloric acid (1.124), boiled from thirty to sixty seconds, or until the chlorin is expelled and a perfectly colorless solution obtained. The liquid is mixed with an equal volume of fuming hydrochloric acid and a few crystals of orcin and boiled again, when in the presence of glycerin a violet or greenish blue coloration will be produced.

Pentoses give the same reaction, but they also reduce Fehling's solution, which glycerin does not.

Sensitive reactions for the detection and identification of glycerin have been described by L. Denigès.[1]

By transforming glycerin with the aid of halogens into dioxyacetone and utilizing the color reactions of this product as well as other properties it is possible to identify glycerin, even when present only in traces. The transformation can be effected either with chlorin or bromin water. The latter being easier obtainable is also preferable.

Put into a test-tube .08 to .1 gram of glycerin or 1 mil of 10 per cent solution of glycerin and add 10 mils bromine water, freshly prepared by shaking vigorously 100 mils of distilled water with .3 mil of bromine in a flask of a capacity of 200 to 250 mils. The shaking should be continued until all bromin is dissolved. The test-tube is then heated on the water-bath for about twenty minutes, and brought to boiling until all bromine has disappeared, then cooled. The mixture, which for convenience shall be called G, is then subjected to the following tests:

[1] Compt. rend., 148, 570, 572.

A—Colorimeter

1. *Direct Reactions.*—Put into four test-tubes .1 mil of an alcoholic solution of the following substances:

A 5 per cent solution of codein.
A 5 per cent solution of resorcinol.
A 5 per cent solution of thymol.
A 2 per cent solution of beta-naphthol.

To the test-tube with codein add .2 mil of G and 2 mils of water. Into the other three tubes put .4 mil of G but no water. To each tube add 2 mils of H_2SO_4 (sp. gr. 1.84); shake and heat only the first and last tubes for two minutes on the boiling water-bath. After about two minutes the following may be observed: A beautiful greenish-blue color and a strong absorption band in red in the tube with codein: an emerald-green color and a greenish flourescence in the tube with β-naphthol, also two absorption bands in the green and red spectrum: a blood-red color in the tube with resorcinol, which becomes reddish yellow or yellow on sufficient dilution with acetic or sulphuric acid, two absorption bands in blue and yellow spectrum; in the tube with thymol a wine red color, changing to rose on dilution.

2. *Reactions in Presence of Potassium Bromide.*—Put into two test-tubes .1 mil of a 4 per cent potassium bromide solution, .4 mil of G, then .1 mil of a 5 per cent alcoholic solution of salicylic acid into one tube, and add an equal quantity of an equally strong solution of guaiacol into the other. Add to each 2 mils of H_2SO_4 (1.84) and heat for two minutes on the water-bath. The tube with salicylic acid will then show an intense violet-red coloration, also two absorption bands in yellow and blue. (Very sensitive and characteristic reaction.) The tube with guaiacol shows an intense blue tinge and an absorptive band in red.

Before attempting to identify glycerin in complex mixtures, it should be separated as completely as possible from the other constituents. The same precaution should be taken in the case of a quantitative estimation.

When working with the liquid preparations, the samples should be concentrated after the addition of a considerable quantity of milk of lime, and the residue extracted several times with absolute alcohol. The combined alcoholic extracts are filtered and treated with $1\frac{1}{2}$ times the volume of absolute ether. After the precipitate has settled, the clear liquid is filtered off, the filter washed with an alcohol-ether mixture of the same proportion as that used for precipitating, and then allowed to evaporate at a moderate temperature. In some instances it will be advantageous to repeat the entire operation, or at least the solution in alcohol and precipitation with ether, using smaller quantities of the reagents.

The glycerin in cold creams and dentifrices can usually be separated

by warming the sample, when the soap and other solid constituents will separate out from the liquid portion.

Estimation of Glycerin.—The amount of glycerin in a mixture of pure glycerin and water may be readily determined from the specific gravity of the mixture and referring to the table.

SPECIFIC GRAVITY OF GLYCERIN AND WATER MIXTURES

Per Cent Glycerin	Sp. Gr. at 15°C. = 59°F.	Per Cent Glycerin	Sp. Gr. at 15°C. = 59°F.	Per Cent Glycerin	Sp. Gr. at 15°C. = 59°F.	Per Cent Glycerin	Sp. Gr. at 15°C. = 59°F.
1	1.00236	26	1.06500	51	1.13265	76	1.20131
2	1.00473	27	1.06765	52	1.13539	77	1.20404
3	1.00711	28	1.07031	53	1.13814	78	1.20677
4	1.00949	29	1.07297	54	1.14088	79	1.20949
5	1.01189	30	1.07564	55	1.14362	80	1.21221
6	1.01430	31	1.07832	56	1.14637	81	1.21493
7	1.01673	32	1.08100	57	1.14912	82	1.21766
8	1.01917	33	1.08370	58	1.15187	83	1.22038
9	1.02163	34	1.08639	59	1.15462	84	1.22310
10	1.02409	35	1.08908	60	1.15737	85	1.22583
11	1.02656	36	1.09176	61	1.16011	86	1.22855
12	1.02904	37	1.09445	62	1.16286	87	1.23128
13	1.03153	38	1.09713	63	1.16561	88	1.23400
14	1.03403	39	1.09983	64	1.16837	89	1.23673
15	1.03653	40	1.10253	65	1.17113	90	1.23945
16	1.03905	41	1.10525	66	1.17387	91	1.24217
17	1.04160	42	1.10798	67	1.17662	92	1.24487
18	1.04416	43	1.11071	68	1.17937	93	1.24756
19	1.04672	44	1.11345	69	1.18212	94	1.25021
20	1.04930	45	1.11618	70	1.18487	95	1.25285
21	1.05189	46	1.11893	71	1.18761	96	1.25547
22	1.05449	47	1.12167	72	1.19035	97	1.25809
23	1.05712	48	1.12441	73	1.19309	98	1.26072
24	1.05973	49	1.12716	74	1.19583	99	1.26335
25	1.06236	50	1.12990	75	1.19857	100	1.26596

Determination of Glycerin in Meat Juices and Extracts. F. C. Cook.[1]—*Acetone Extraction Method.*—Weigh approximately 2 grams of a solid or 5 grams of a liquid meat preparation in a small lead dish containing 20 grams of ignited sand. Transfer the lead dish and its contents to mortar containing more ignited sand and several grams of anhydrous sodium sulphate and mix thoroughly. Transfer the lead dish and the sand to a Soxhlet apparatus which has a piece of cotton placed in the side arm to prevent the siphoning over of sand, etc. Extract the entire mass with

[1] J. Assoc. Off. Agri. Chem., 1915, 1, 279.

redistilled anhydrous acetone for ten hours; distill the acetone, carefully removing the last trace by means of a vacuum pump; take up the glycerin in water, add a little silver nitrate, make to 100 mils volume, let stand overnight, filter, and oxidize a portion of the filtrate according to the dichromate method of Hehner.

Hehner's Dichromate Method for Glycerol.—One part of glycerol is quantitatively oxidized to carbonic acid by 7.486 parts of dichromate in the presence of sulphuric acid. The solutions required are:

Standard Potassium Dichromate.—74.86 grams of pure potassium dichromate are dissolved in water, 150 mils of concentrated sulphuric acid added, and when cold, diluted to a liter. One mil = .01 gram glycerol.

A weaker solution is also made by diluting 100 mils of the strong solution to a liter.

These solutions should be controlled by a ferrous solution of known strength, if there is any doubt about the purity of the dichromate.

Solution of Double Iron Salt.—240 grams of ferrous ammonium sulphate are dissolved with 50 mils of concentrated sulphuric acid to a liter, and its relation to the standard dichromate must be accurately found from time to time by titration with the latter, using the ferricyanide indicator.

Method of Procedure.—With concentrated or tolerably pure samples of glycerin it is only necessary to take a small weighed portion, say 0.2 gram or so, dilute moderately, add 10 or 15 mils of concentrated sulphuric acid and 30 or 40 mils of the stronger dichromate, place the beaker covered with a watch-glass in a water-bath and digest for two hours; the excess of dichromate is then found by titration with the standard iron solution. The weaker dichromate is useful in completing the titration where accuracy is required. As the stronger dichromate and the iron solution are both concentrated, they must be used at a temperature as near 15° C. as possible. If the operation be carried out on a water-bath and kept at normal temperature during the operation no correction will be necessary. In the case of crude glycerin it must be purified from chlorin or aldehyde compounds as follows: About 1.5 grams of the diluted sample is placed in a 100-mil flask, some moist silver oxide added, and allowed to stand ten minutes. Basic lead acetate is then added in slight excess, the measure made up to 100 mils, filtered through a dry filter, and 25 mils or so digested with excess of dichromate, and titrated as before described.

Determination of Glycerin in Pharmaceutical Preparations.—If the sample is a paste, cream or emollient, weigh out 10 grams, add water and bring to a uniform mixture, and then transfer to a 500-mil graduated flask, render slightly acid with hydrochloric acid, and make up to the mark.

With the liquid products use a sample of 10–50 mils, depending on the concentration.

Filter off 100-mil aliquots, concentrate to about 15 mils, add 5–10 grams of clean uniform sea sand, 5–10 mils of milk of lime (containing about 15 per cent CaO) and evaporate to pastry consistency. Treat the moist residue with 50 mils of 90 per cent alcohol (by volume) remove the substance adhering to the sides of the dish with a spatula and rub the whole mass to a paste. Heat the mixture on a water-bath to incipient boiling, stirring constantly, and decant the liquid through a filter into an evaporating dish. Wash the residue by decantation, with 10-mil portions of hot 90 per cent alcohol, until the filtrate amounts to 150 mils. Evaporate the filtrate to syrupy consistency at a temperature below the boiling-point of water; transfer the residue to a small glass-stoppered, graduated cylinder with 20 mils of absolute alcohol and add three portions of 10 mils each of anhydrous ether, shaking after each addition. Let stand until clear, then pour off through a dry filter, wash cylinder and filter with a mixture of one part absolute alcohol and $1\frac{1}{2}$ parts of anhydrous ether. Evaporate the filtrate to syrupy consistency and immediately remove from warm bath.

Dissolve in water, transfer to a larger beaker and add enough water to measure about 400 mils. Add 10 grams potassium hydroxide and an excess of potassium permanganate either in the form of a saturated solution or as crystals. An excess is present when the liquid is no longer green, but shows a bluish or magenta color. Boil one hour, then add drop by drop a saturated solution of sodium sulphite until solution is just decolorized. Transfer contents of beaker to a 500-mil graduated flask, washing out with hot water, and making up to 515 mils to allow for the hot water and precipitate. Filter hot through a dry filter, leaving precipitate unwashed, and cool to room temperature; 400 mils of the filtrate are made acid with acetic acid, an excess of calcium chloride added, and allowed to stand in a warm place for three hours. Then filter, wash with hot water, transfer precipitate to a flask with as small a quantity as possible of water, add 10 mils concentrated sulphuric acid, and titrate with N/10 permanganate.

One mil N/10 permanganate = .0046 gram glycerin.

The method depends on the oxidation of the glycerin to oxalic acid, and the subsequent precipitation of the latter as calcium oxalate. The latter should be titrated and not ignited and weighed as CaO, as it may be contaminated with sulphate, silicate, and other impurities.

MANNITOL

The most important polyhydric alcohol from the point of view of the drug chemist is mannitol or mannite. It is a reputed constitutent of manna, a concrete saccharine exudation of Fraxinus ornus (Oleaceæ), a species of ash growing in the Mediterranean countries and Asia Minor.

Mannitol has the composition

$$CH_2(OH)CH(OH)CH(OH)CH(OH)CH(OH)CH_2OH.$$

It is a colorless, crystalline substance, with a sweet taste, soluble in water and hot alcohol, but insoluble in ether. It exists in several modifications, differing principally in their optical properties. It does not reduce Fehling's solution.

Manna

Manna is credited with possessing laxative, demulcent, expectorant, and nutritive properties and will occur in remedies for constipation and coughs which are especially recommended for children. It is usually administered with other laxative drugs such as senna, rhubarb, magnesium sulphate, and Rochelle salts.

Manna is composed of several carbohydrates, among which have been identified levulose, dextrose, mannotriose, and mannotetrose, mannite or mannitol, small amounts of resin and ash, and about 10 per cent of moisture. Tanret gives the mannitol content at from 40–55 per cent.

The authorities administering the Food and Drugs Act require a manna to contain not less than 75 per cent of material soluble in 90 per cent alcohol. This material soluble in 90 per cent alcohol was formerly considered to consist chiefly, if not entirely of mannitol, but recent investigations show that this conclusion is erroneous. Lawall and Forman [1] have reported a comparison of several samples of manna with pure mannitol.

	Mannite: pure crystals	Suspicious sample	Sample of so-called high grade manna purchased in open market	Sample of large flake manna at least twenty-five years old	Sample of small flake manna at least twenty-five years old	Sample of large flake manna over thirty years old
*Polarization of whole manna before inversion	0°	73.5°	72.8°	73.8°	78.0°	45.8°
Polarization of same after inversion	0°	52.9°	39.5°	59.2°	51.5°	37.2°
Reducing sugars before inversion	None	17.10%	13.2%	17.7%	10.8%	11.3%
Reducing sugars after inversion	None	36.4%	32.6%	26.6%	26.8%	16.6%
Per cent soluble in 90 per cent alcohol	Entirely soluble	68.8%	90.5%	93.7%	77.9%	96.7%

* All of the polarization figures are sugar scale readings in a 200-mm. tube, using 26 grams in 100 cc. of solution.

[1] J. Amer. Pharm. Ass., 1917, 22.

	Mannite: pure crystals	Suspicious sample	Sample of so-called high grade manna purchased in open market	Sample of large flake manna at least twenty-five years old	Sample of small flake manna at least twenty-five years old	Sample of large flake manna over thirty years old
Polarization of alc. sol. ext. before inversion	0°	65.3°	55.1°	44.5°	insuf. material	57.3°
Polarization of same after inversion	0°	51.5°	35.5°	32.3°	insuf. material	45.6°
Reducing sugars in alc. sol. ext. before inversion	None	15%	16.4%	11.6%	insuf. material	18.7%
Reducing sugars in same after inversion	None	30.3%	33.2%	23.1%	insuf. material	23.9%
Melting-point	163° C.	131° C.	123° C.	140° C.	140° C.	140° C.
Charring with strong H_2SO_4	None	Slight	Slight	Slight	Slight	Very Slight
Fermentation test with yeast	Negative	Positive	Positive	Positive	Positive	Positive

The Bureau of Chemistry in S. R. A. 16, issued Jan. 26, 1916, under article 162 sets down the following tentative standard for manna: Manna (the dried saccharine exudation of Fraxinus ornus Linne. Fam. Oleaceæ) occurring in irregular, more or less elongated, flattened, three-sided pieces; externally, yellowish white, friable, somewhat waxy; internally, whitish, porous, and crystalline in appearance; odor suggestive of maple sugar; taste sweet, slightly bitter, and faintly acrid; it should not consist of soft, brownish, viscous masses full of impurities, known as fat manna. Mannite (soluble in 90 per cent alcohol) not less than 75 per cent; moisture (loss at 100° C.) not more than 10 per cent; ash not more than 3 per cent; acid-insoluble ash not more than 1 per cent.

Recently Furlong and Campbell [2] have reported a manna-like incrustation on a species of Gymnosporia from Northwestern Rhodesia. This product had a slightly sweet taste, and was found to contain 4.9 per cent of moisture, 54 per cent of dulcitol, 6.4 per cent of reducing sugar, and 6.6 per cent of sucrose. The melting-point of the dulcitol was found to be 183° (uncorrected) and 188° C. (corrected.)

Manna-like substances occur on many other species of vegetation and have been reported from time to time usually with the designation of the country or locality from which they are derived.

[2] Chem. Soc. Proc., 1913, 29, 128.

AROMATIC AND TERPENE ALCOHOLS

The true aromatic alcohols are those substances with an hydroxyl group in the side chain and their general properties bear a close relationship to those of the aliphatic series. The introduction of an hydroxyl into the nucleus produces an entirely different group of substances known as phenols.

The aromatic alcohols may be prepared by heating the corresponding halogen derivatives with water, weak alkali or silver hydroxide, by reducing the corresponding aldehydes or ketones, and in certain instances by treating the corresponding aldehydes with potash.

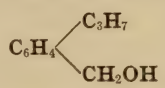
The straight aromatic alcohols are of little importance in drug chemistry, except as they furnish a means of identifying the aromatic balsams. Benzyl and cinnamyl alcohols occur in these substances in the form of their benzoic and cinnamic esters.

Of great importance, however, is the terpene alcohol menthol. and to a lesser extent borneol.

Ortho-oxybenzyl Alcohol, $C_6H_4(OH)CH_2OH$

This body, known also as Diathesin, occurs in fine crystals, melting 86°, soluble in water and alcohol, and used as an analgesic, antipyretic, and antirheumatic. It possesses phenolic properties due to the hydroxyl attached to the nucleus.

Cuminic or paraisopropyl benzyl alcohol



This is a colorless liquid with a burning taste, boiling 246° C., sp. gr. .977 at 15° C., readily soluble in alcohol and ether. It may be prepared by treating cuminic aldehyde with alcoholic potash. Cuminic aldehyde or cuminol is one of the constituents of the oil of Roman Chamomile.

Cinnamyl Alcohol, $C_6H_5CH{=}CHCH_2OH$

Cinnamyl alcohol is obtained by the hydrolysis of cinnamyl cinnamate or styrene. It crystallizes in needles, having a hyacinth odor, melting 35°, boiling 250°, sparingly soluble in water, but readily in alcohol and ether. When slowly oxidized in the presence of platinum black it is converted to cinnamic aldehyde and finally to cinnamic acid.

Salicyl Alcohol, $C_6H_4(OH)-CH_2OH$

Salicyl or hydroxybenzyl alcohol is a di-substituted benzene and can exist in three different forms. The 1–2 derivative is saligenin, obtained

by the hydrolysis of salicin. It is crystalline substance, melting 82°, subliming 100° readily soluble in alcohol and ether, and less readily in water. On oxidation it yields salicylous aldehyde and salicylic acid. It gives an intense blue color with ferric chloride. Owing to its phenolic nature it forms alkali salts which when heated with alkyl halogen compounds yield the corresponding ethers.

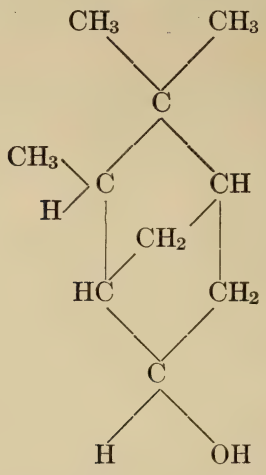
The meta compound melts 67° and the para 110°.

Anisyl Alcohol, $C_6H_4(OCH_3)CH_2OH$

This alcohol is obtained on treating anisic aldehyde with sodium amalgam or alcoholic potash. It melts 25° and boils 258°.

Borneol

Borneol occurs in the free state and in the form of esters in the oils of many different plants. The borneo-camphor from Dryobalanops camphora consist of *d*-borneol. The same modification occurs in spike and rosemary oils. The *l*-form occurs as esters and also in the free state in the oils of citronella, Matricaria parthenium, valerian, and kousso. The acetate has a characteristic fir odor and is present in many coniferous oils.



Borneol crystallizes in laminæ and plates, melting 203–204° boiling 212°. Its odor is similar to camphor and also resembles amber. Both modifications are alike in their chemical properties. On oxidation with chromic acid it yields camphor, and with nitric acid camphoric acid results. Phosphorus pentachloride converts it into bornyl chloride, and on boiling the latter with anilin, camphene is produced. It is very stable towards dehydrating agents such as zinc chloride and sulphuric acid, differing

thereby from the isomeric isoborneol. It forms addition products with chloral and bromal, the former melting at 56° and the latter 105–109°.

Borneol can be separated from camphor by heating with succinic acid anhydride. The sodium salt of the ester produced is soluble in water and therefore easily separated from camphor. The corresponding derivatives of phthalic acid may be used.

Bornyval

Bornyval is borneol isovalerate, $CH_3CH(CH_3)CH_2COO \cdot C_{10}H_{17}$, the isovaleric acid ester of borneol.

Borneol isovalerate is a clear aromatic liquid, having an odor resembling oil of rosemary and at the same time a weak odor and taste of valerian. It is insoluble in water, but dissolves in all proportions of alcohol and ether. The liquid boils at 225° to 260° C. under ordinary pressure. At a pressure of 50 mm. it boils at 150° to 170° C., its specific gravity is .945 to .951; it is lævorotatory, the angle of rotation lying between −30° and 32° in a 100-mm. tube at 20° C.

It is said to be useful in the various neuroses.

Gynoval

Gynoval is isoborneol isovalerate, $CH_3CH(CH_3)CH_2COO \cdot C_{10}H_{17}$, the isovaleric acid ester of isoborneol.

It is a colorless neutral fluid of a peculiar aromatic odor and mild oleaginous taste. It is difficultly soluble in water, but easily dissolved in alcohol, ether, acetone, chloroform, benzol, and petroleum-benzine. It boils at 132° to 138° C., under 12 mm. pressure, and has specific gravity of .952–.957 at 15 °C.

Gynoval dissolves in concentrated sulphuric acid with formation of a red-brown color and liberation of an odor of sulphurous and valeric acids. On heating glynoval with an alcoholic solution of potassium hydroxide for several hours on a water-bath it is completely split up into its components, and on diluting this saponification liquid, isoborneol separates in solid form, while potassium valerate remains in solution.

The action of gynoval is that of a mild nervine and antispasmodic, resembling that of valerian.

Brovalol, $CH_3CH(CH_3)CHBrCOO(C_{10}H_{17})$

Brovalol is bornyl brom-valerate, a colorless oily liquid having a slight aromatic odor, boiling at 163° under 10-mm. pressure, insoluble in water but soluble in alcohol, ether, and chloroform.

It acts as a nervine.

Menthol, $C_{10}H_{19}OH$

Menthol is a saturated secondary alcohol, and the chief constituent of peppermint oils from Mentha arvensis and M. piperita.

It is used to a large extent in medicinal preparations. It will be found in antiseptics, refrigerants, stimulants, and carminatives, and is almost always a constituent of the numberless gargles, mouth washes, and antiseptic liquids in daily household use. It will be found in tooth pastes, in ointments recommended for colds, sore throat, catarrh, headache, neuralgia, earache, toothache, piles, chapped hands, hay fever, insect bites, and in liniments.

Tablets and powders intended for antiseptics will be composed of menthol with one or more sodium or potassium salts, borate, bicarbonate, chloride, sulphate, phosphate, benzoate, and salicylate with perhaps eucalyptol, thymol, and methyl salicylate. Mentholated throat tablets contain menthol, cocain, oil of anise, eucalyptol, and benzoic acid. The antiseptic liquids of the "listerine" type contain menthol, eucalyptol, methyl salicylate, thymol, boric acid and Baptisia tinctoria, Wild Indigo, and sometimes formaldehyde and its derivative; those of the "glycothymoline" type contain borates, bicarbonates, benzoates, glycerin, eucalyptol, thymol, menthol, Pinus pumilio, colored with cudbear, and in certain instances other ingredients.

Liniments may contain a great variety of substances and with menthol there may occur one or several of the following: camphor, cantharides, capsicum, thujone, turpentine, sassasfras, rosemary, thyme or mustard oils, aconite, belladonna, opium, potassium iodide, iodin, mercury salts, ammonia, in a menstruum of alcohol, chloroform, acetone, alcoholic soap, some fixed oil, glycerin or acetic acid.

Tooth powders may contain menthol, myrrh, cassia oil, sassafras, eucalyptol, thymol, methyl salicylate, calcium carbonate and phosphate, magnesium carbonate or oxide, calcium peroxide, or magnesium, orris root, with and without soap. Practically the same constituents will be found in some combination or other in tooth pastes, to which in addition, glycerin and coloring matter are added.

Ointments containing menthol vary in the character of the other materials, depending on the uses to which they are to be put. Ointments of menthol, camphor, and boric acid in a petroleum vehicle have a wide application; ointments with menthol, mustard oil, and aromatic balsams in lard constitute another class, and again we find a heterogeneous collection embracing menthol, camphor, phenol, turpentine, quinin, and opium, in stearic acid recommended for croup, pneumonia, and similar ailments. There are many types of formulas, but it would be impossible to note all the combinations which are offered. Some of them are exploited with

special stress laid on some one ingredient, and some will consist of the ordinary antiseptics and refrigerants with an unusual substance added to give it the unique character assigned to it. It is sufficient to conclude by saying that menthol will be found in nearly all of them.

Menthol crystallizes in colorless acicular or prismatic crystals, having a characteristic odor and a warm aromatic taste followed by a sensation of cold when air is drawn into the mouth. It melts 43° C., boils 212°, is only slightly soluble in water, but dissolves readily in all the organic solvents. When triturated with an equal weight of thymol, camphor, or chloral hydrate there results a liquid mixture.

Menthol is lævogyrate, as it occurs in nature and the commercial article is always of this character. Its rotation is -49.30 in 20 per cent alcoholic solution or $-57.7°$ in 10 per cent alcoholic solution. When oxidized with chromic acid a lævo ketone, menthone, $C_{10}H_8O$, results. With permanganate the oxidation goes further with formation of keto-methylic and β-methyladipinic acids, the latter melting 88–89°.

On heating menthol with benzoic acid anhydride, menthyl benzoate is produced. This ester is difficultly volatile with steam and melts 54–55°.

Menthol has such unique properties that no special directions are needed to identify it. Its odor is usually sufficient to determine its presence. However, when it occurs in mixtures containing camphor it may easily be overlooked, because if the camphor is in excess (and it usually is), the odor of the menthol is completely overlooked. It is difficult to separate menthol from camphor.

U. S. P. Method for Determination of Menthol in Oil of Peppermint.—Introduce 10 mils of the oil into a flask provided with a ground-glass tube-condenser (acetylization flask), add 10 mils of acetic anhydride and about 1 gram of powdered anhydrous sodium acetate, and boil the mixture gently during one hour. Allow it to cool, wash the acetylized oil with distilled water, and afterward with sodium carbonate T. S., diluted with an equal volume of distilled water, until the mixture is slightly alkaline to phenolphthalein T. S., and then dry it with the aid of fused calcium chloride, and filter. Transfer 5 mils of the dry acetylized oil to a tared 100-mil flask, note the exact weight, add 50 mils of half-normal alcoholic potassium hydroxide V. S., connect the flask with a reflux condenser, and boil the mixture during one hour. After cooling, titrate the residual alkali with half-normal sulphuric acid V. S., using phenolphthalein T. S. as indicator, and calculate the percentage of menthol present by the following formula:

$$\text{Percentage of menthol} = \frac{A \times 7.808}{B - (A \times 0.021)}$$

in which A is the result obtained by subtracting the number of mils of half-normal sulphuric acid V. S. required in the above titration from the

number of mils of half-normal alcoholic potassium hydroxide V. S. originally taken, and B is the weight of acetylized oil taken.

Coryfin

Coryfin is menthyl ethylglycolate, $CH_2(O \cdot C_2H_5) \cdot COO(C_{10}H_{19})$, the ethylglycolic acid ester of menthol. It is a limpid, colorless oil, having a very faint menthol odor, boiling under 20 mm. pressure at about 155° C., soluble in alcohol, ether, and chloroform; difficultly soluble in water.

When heated with caustic alkalies it is split up into menthol and ethylglycolic acid.

Coryfin is used as a substitute for menthol.

Validol

Validol is menthyl valerianate, $CH_3CH_2CH_2COOC_{10}H_{19}$, with about 30 per cent of free menthol.

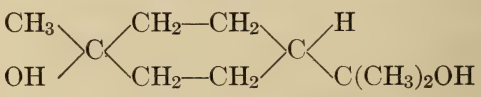
It is a clear, colorless liquid, of the consistency of glycerin, having a mild pleasant odor, distinct from either that of menthol or valerian, and a refreshing cool and very faintly bitter taste, insoluble in water, but readily soluble in alcohol, ether, chloroform, and oils. It is decomposed by alkalies. On warming with sodium hydroxide solution, the odor of menthol manifests itself; if then the alkaline solution is acidulated with diluted sulphuric acid, the odor of valerianic acid is developed.

Forman, or Chlormethyl Menthyl Ester, is described in full under formaldehyde.

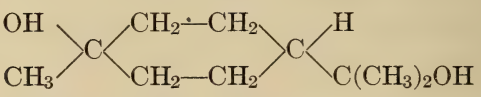
Estoral is the name given to so-called boric acid menthol ester, which is evidently a weak compound, for it is decomposed into its constituents by the action of water. It is used in chronic nasal catarrh.

DIACID ALCOHOLS

Terpine, $C_{10}H_{18}(OH)_2$, exists in two forms cis-terpine and trans-terpine. The former may be represented by the structure



the latter



The former readily adds H_2O and becomes terpin hydrate, from which it may be prepared.

Cineol or Eucalyptol may be regarded as the oxide corresponding to this form.

Cis-terpine melts at 104° and boils 258° C.

Terpin hydrate is the product which is of special interest to the drug chemist. It is prepared by acting on turpentine, under proper conditions, with alcohol and nitric acid, or by the use of hydrogen peroxide, and is a colorless, lustrous crystalline body, $C_{10}H_{18}(OH)_2+H_2O$, with a slight aromatic odor and a somewhat bitter taste, melting 116–117° when rapidly heated. It loses its water of crystallization when heated for a prolonged period at 100°, and sublimes at the same temperature.

Terpin hydrate is somewhat soluble in water, chloroform, and ether and dissolves with ease in hot water, alcohol, and glacial acetic acid.

Cineol, $C_{10}H_{18}O$

Cineol or Eucalyptol may be prepared from terpin hydrate under suitable conditions, but its interest to us lies in the fact that it is an important constituent of the oils of Eucalyptus.

It is a colorless liquid with a characteristic camphoraceous odor, and a pungent cooling taste. It boils 176–177° C., and on exposure to a low temperature crystallizes into a mass of needles, melting −1° C. Its specific gravity is .930 at 15° or .921–.923 at 25°. It is optically inactive. It is soluble in all of the ordinary organic solvents, fixed and volatile oils, but does not dissolve in water, nor in solutions of the alkalies.

Cineol is probably an oxide. It gives none of the characteristic reactions of the common classes of organic bodies. It does, however, give a number of characteristic reactions, some of which are valuable in its identification and estimation. When exposed to a freezing mixture and treated with an equal volume of syrupy phosphoric acid, it yields a phosphate which may be decomposed by hot water with regeneration of cineol.

With bromin, cineol forms $C_{10}H_{18}OBr_2$, which crystallizes in red needles; this bromin compound decomposes with ease yielding water, bromin, and cineol.

With a saturated solution of iodin in potassium iodide, cineol yields a mass which contains green lustrous deliquescent crystals.

Cineol reacts with iodol to form a crystalline compound, melting 112°. It may be obtained by shaking the sample with the reagent until it is dissolved and then warming. As soon as the crystalline addition produced separates, it may be separated and recrystallized out of alcohol or benzol.

When shaken with a fairly strong solution of resorcinol, cineol soon forms a white solid which falls to the bottom of the container.

Dry hydrochloric acid gas conducted into a mixture of equal volume of cineol and petroleum ether gives a crystalline precipitate of an unstable hydrochloride.

When oxidized with a warm solution of potassium permanganate cineol gives dibasic cineolic acid, $C_{10}H_{16}O_5$, melting 196–197°.

The presence of cineol in medicinal products is usually apparent by the odor. If it is desired to separate it from a mixture such as a mouth wash or inhalant, the sample should be diluted with water and subjected to steam distillation, by which treatment the volatile constituents will be carried over into the receiver and separated from any salts, glycerin fixed oils, and other non-volatile substances. The distillate is cooled and shaken out with petroleum ether and the solvent separated, dried with calcium chloride, and then filtered and subjected to a stream of dry hydrobromic or hydrochloric acid which will threw out the cineol. After decanting and washing with petroleum ether, the crystals may be treated with water and the cineol freed.

For the determination of cineol in the oils of Eucalyptus there are two types of procedures recommended, one depending on the absorption of cineol by phosphoric acid, and the other the combination of cineol and resorcinol. Each method has its own advocates.

The method of the U. S. Pharmacopœia is of the first type.

Measure 10 mils of the oil, from a pipette, into a round-bottom glass dish of 50-mils capacity, which is imbedded in finely broken ice. Add 10 mils of arsenic acid T. S. and stir until precipitation is complete. When the mixture ceases to congeal further, allow it to stand for ten minutes in the ice bath. (If at this point a hard mass is formed, add 5 mils of purified petroleum benzin, and mix the mass well before proceeding with the assay.) Then transfer it immediately to a hardened filter paper, about 18.5 cm. in diameter, by means of a pliable horn spatula; spread it evenly over the surface of the paper and lay a second hardened filter paper over the top. Wrap several thicknesses of absorbent or filter paper around the hardened filters, and place the whole between the plates of a press and bring to bear all the pressure possible for about one minute. Change the outside absorbent papers and press again, repeating the operation, if necessary, until the eucalyptol arsenate is apparently dry, and separates readily when touched with a spatula. The pressing is not complete when a hard mass remains which is broken up with difficulty; and usually two changes of filter paper are required, pressing each time for about two minutes; if left too long in the press the compound may decompose. Now, transfer the compound completely by means of the horn spatula to a glass funnel inserted into a 100-mil cassia flask with a neck graduated to 10 mils into tenths. Wash the last portions of the precipitate into the flask with a stream of hot distilled water from a wash bottle, assisting the disintegration with a glass rod, place the flask in boiling water and rotate it until the compound is thoroughly broken up. Then add enough distilled water to cause the eucalyptol to rise into the

neck of the flask, cool it to room temperature and read its volume. This volume, multiplied by 10, shows the percentage of eucalyptol (cineol) in the oil.

The following method, which depends upon the solubility of the resorcin-eucalyptol in excess of solution of resorcin, is stated to give results more accurate than the phosphoric acid method usually employed. Ten mils of the essence is introduced into a 100-mil Hirschsohn flask and well shaken up with about 80 mils of 50 per cent solution of resorcin for five minutes, the non-soluble portion of the oil is allowed to separate, then more resorcin solution is added to bring the non-cineol portion into the graduated portion of the neck, when its volume is read off. Oils which are very rich in cineol should first be diluted with an equal volume of essential oil of turpentine, or the cineol-resorcin compound will crystallize out, and in so doing retain some of the non-cineolic constituents. Obviously in this case the volume of the liquid read off must be multiplied by 2 to give the percentage. Not only is the method more accurate and convenient, but by mere distillation or evaporation, the resorcin cineol compound is decomposed; the residual resorcin, evaporated to dryness, may be used again for another cineol determination.

Eucalyptol enters into the composition of a number of popular remedies, including mouth washes and gargles and catarrh and hay fever remedies of the hyomei type. Its presence in most of these mixtures is apparent by the odor. It is also a component of tablets of the same general composition as the gargles and douches, and is dispensed with sandal-wood oil and creosote in capsules.

ETHERS

Ethers are related to the metallic oxides in the same way as the alcohols are related to the metallic hydroxides. CH_3OH corresponds to KOH and CH_3OCH_3 corresponds to KOK. The term "ether" is also applied to the esters of acetic and other acids, but these are, strictly speaking, ethereal salts, and will be considered in their proper place in a subsequent chapter.

With the exception of methyl ether, which is a gas, they are mobile, volatile inflammable liquids, lighter than water and boiling at a lower temperature than the corresponding alcohols. They are even more inert than alcohols, as they are not acted upon by alkalies of alkali metals or by phosphorus pentachloride in the cold. They do not combine with dilute acids, but when heated they yield ethereal salts with the elimination of water, and form substitution products with chlorine and bromin.

Ethyl or Sulphuric Ether, $C_2H_5OC_2H_5$

Ethyl ether is the only substance of this class which is of importance in our work, and as it is used almost entirely as an individual, and but seldom in mixtures, the question of its determination is not of great moment. For its identification its inertness and failure to give characteristic reactions for alcohols, aldehydes, and ketones in conjunction with its physical tests are sufficient.

The analyst will often be called upon to determine the availability of a sample for anesthetic purposes, and in pharmaceutical establishments to pass upon its quality for manufacturing; and in special cases for a reagent in high-grade analytical work.

The established grades of ether include:

Anhydrous ether, which is practically pure ethyl oxide.

Anesthetic ether, which complies with the requirements of the Pharmacopœia which may contain alcohol up to 4 per cent and traces of acetaldehyde, acids, and water.

Commercial ether, which contains at least 95 per cent by weight of ethyl oxide.

For some purposes one will encounter:

Ether U. S. P. 1880, called " 80 ether," composed of about 74 per cent of ethyl oxide and 26 per cent alcohol containing a little water, specific gravity .750 at 15° C.

Stronger ether U. S. P. 1880 containing 94 per cent ethyl oxide and about 6 per cent of alcohol containing a little water, specific gravity .716 at 25° C.

Ether composes about one-third of Spirit of Ether and of Compound Spirit of Ether or Hoffmann's Anodyne. It is also present in some ethereal tinctures, lobelia, ferric chloride, valerian, belladonna, etc.

Dr. Chas. Baskerville and Dr. W. A. Hamor [1] have made an exhaustive study of ether and devised a scheme for the examination of the product for analytical and anesthetic purposes with particular reference to the detection of avoidable impurities. The standards adopted by these gentlemen and the procedures to be employed for determining the necessary data are quoted herewith.

1. *Specific Gravity.*—Determine the specific gravity by means of a pyknometer at 15° C.

2. *Boiling-point.*—In the case of anesthetic ether, at least 97 per cent of the sample should distill over between 34° and 36° C. (at 760 mm.), and none of it should come over above 37°; after the fractionation to this temperature, no residue should remain in the fractionating vessel.

[1] J. Ind. and Eng. Chem., 1911, 3, 301 and 378.

In the case of the anhydrous ether, at least 99.50 per cent should distill off between 34° and 36°, and none should come over above 36°.

3. *Organic Impurities.*—When 20 mils of the sample are added drop by drop to 20 mils of pure concentrated sulphuric acid, which is kept cooled during the tests and which is contained in a glass-stoppered bottle previously rinsed with concentrated sulphuric acid, the resulting solution should be colorless. The sulphuric acid should be gently shaken after the addition of each drop of ether in order to ensure perfect solution.

4. *Odor.*—When 50 mils of the sample are allowed to evaporate spontaneously on filter paper, 10 cm. in diameter, contained in a flat porcelain dish, the paper should be odorless after the evaporation of the ether. The latter should be added to the paper in portions in such a manner as completely to moisten it. In the case of a decided odor being imparted to the filter paper, the ether should be rejected, but for further information may be tested for such impurities as " heavy oil of wine," fusel oil, etc.

5. *Residue* (*Extractive Matter, Odor and Acidity*).—(1) When 25 mils of the sample are allowed to evaporate spontaneously in a clean, dry glass dish, the moist residue must possess no odor, and must neither redden nor bleach blue litmus paper; this residue must evaporate completely on a water-bath—that is, there should be no fixed residue.

(2) 100 mils of the ether under examination are allowed to spontaneously evaporate in a flask until about 15 mils remain in the vessel. This residue should be free from color and foreign odor, and should comply in full with the following tests: (*a*) When 5 mils are allowed to evaporate at room temperature after the addition of 2 mils of water, the residue should neither redden nor bleach sensitive light-blue litmus paper. (*b*) When another portion of 5 mils is allowed to evaporate on a 9-cm. filter paper contained in a porcelain dish, there should be perceptible no foreign odor (amyl compounds, empyreumata, pungent matters, etc.) as the last portions disappear from the paper, and the latter should be left odorless. (*c*) On the addition of the remaining 5 mils to 5 mils concentrated sulphuric acid, kept cool during the test and contained in a glass-stoppered tube previously rinsed with concentrated sulphuric acid, there should result no perceptible coloration. Anesthetic ether should comply in full with these tests.

6. *Acidity.*—(1) When 25 mils of the sample are allowed to evaporate at room temperature after the addition of 5 mils of pure water the residue should neither redden not bleach sensitive light blue litmus paper.

(2) When 20 mils of pure ether are shaken with 10 mils of pure water and 2 drops of phenolphthalein, the same depth of color should result on adding an equal amount of N/100 potassium hydroxide solution as in a test using pure water alone. In the case of ether intended for special analytical purposes, the addition of .3–.5 mil of N/100 potassium hydroxide

should produce an alkaline reaction. When more than 1 mil is required, the ether should be rejected for anesthetic purposes.

7. *Water and Alcohol* (*Exclusion Tests for Pure and Anhydrous Ethers*). (1) (This test is superfluous if the ether possesses a correct specific gravity.) A minute quantity of powdered fuchsin (rosaniline acetate), previously dried at 100° C., is placed in a dry test-tube, 10 mils of the ether are added, and the tube is corked and shaken well. In the case of pure and anhydrous ethers, no amethystine color—even faint—should result. If the coloration imparted to the ether is considerable, the approximate percentage of impurity is determined by Allen's method.[1]

(2) When several milligrams of anthraquinone and the same amount of sodium amalgam are added to 10 mils of the ether there should result no formation of red or green substances. The presence of both water and alcohol may be detected by this test.

8. *Water* (*Exclusion Tests for Pure and Anhydrous Ethers*).—(1) On shaking 1 gram of anhydrous copper sulphate with 20 mils of ether, the salt should not assume a green or blue color.

(2) In important or doubtful cases, the test with amalgamated aluminum may be used. If the ether contains no moisture and it responds to the tests under " Water and Alcohol " the presence of the latter may be really assumed, especially if the colors are marked.

9. *Water and Aldehyde* (*Exclusion Test for Pure and Anhydrous Ethers*).—When 15 mils of the sample are placed in a perfectly dry test-tube and a piece of metallic sodium about 5 mm. in diameter is added, there should result only a slight evolution of gas and the sodium should not possess, after standing six hours, a white or yellow coating and the ether should not be colored or turbid. Only when the ether has been previously treated with sodium will the latter retain a distinct metallic luster at the expiration of the test; otherwise the metal becomes coated with sodium hydroxide. In the presence of aldehyde the sodium hydroxide is more or less colored.

10. *Acetaldehyde.*—(1) Apply the fuchsin-sulphurous acid test of Francois. Pure ether should not restore the color to fuchsin decolorized by sulphurous acid. The red-violet color should be faint in the case of anhydrous ether.

(2) On covering 5 grams of solid potassium hydroxide, in freshly broken pieces about 5 cm. in diameter, with 30 mils of the sample, and allowing the mixture to stand for six hours, tightly closed and protected from the light, and occasionally shaking, the potassium hydroxide should

[1] All colorimetric tests should be performed preferably with a colorimeter, having tubes with an internal diameter of 1.5 cm. But other forms of vessels may be used; for example, a ground-glass-stoppered Erlenmeyer flask, of suitable size for the amounts of liquid prescribed in the test, has been found to answer.

not acquire a yellowish color, no yellowish or brown colored substance should separate, and the ether should not become turbid or assume any color. This is recommended as the exclusion test for anesthetic ether. Pure or anhydrous ether should give no response after standing twenty-four hours.

(3) In the absence of alcohol, as indicated by these tests for water and alcohol, and confirmed by those given below, the following test may be applied for the detection of aldehyde: When 10 mils of the sample are agitated with 2 mils of Nessler's solution, a yellow color or black precipitate is indicative of the presence of aldehyde. Pure ether is indifferent toward this reagent, but it is impossible to purchase ether which does not show a yellow color within fifteen minutes. For anhydrous or anesthetic ether, it is sufficient to require, therefore, that no black precipitate settles out, although the mixture may assume an opalescent yellow color.

11. *Alcohol.*—The occurrence of alcohol may be ascertained as follows:

(1) In the presence of water, a portion of the sample is dried over anhydrous potassium carbonate and then tested, in 10-mil portions, with (*a*) rosaniline acetate, and (*b*) anthraquinone sodium amalgam.

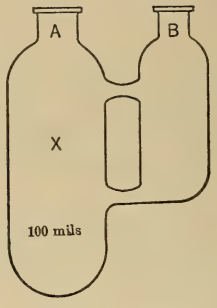
(2) In the absence of other than mere traces of acetaldehyde, by Lieben's iodoform test.

(3) In the presence of acetaldehyde, by this method: The amount of aldehyde in 25 mils is approximately determined colorimetrically by Francois method. A portion of 25 mils is then agitated with 25 mils pure water in a ground-glass-stoppered bottle, and the aqueous layer, which will show an increase in volume greater than 10 per cent of the ether taken depending on the amount of alcohol present, is removed and freed from dissolved ether by careful warming at 40° C., until ether is expelled. The alcohol in the water is then oxidized by potassium dichromate and sulphuric acid, the aldehyde produced is distilled off, and the amount contained in the distillate is determined approximately colorimetrically. By comparison with the percentage of aldehyde found as originally existing in the ether, the amount of alcohol may be calculated; however, the authors do not recommend the method as an exact quantitative one, but only as one for arriving at the approximate amount of alcohol contained in ether, and as a confirmatory test.

12. *Peroxides* (*Exclusion Test for Ether of all Grades*).—When 2 mils of a 10 per cent cadmium potassium iodide solution are well shaken with 10 mils of the sample, there should result no liberation of iodin within one hour. This may be easily determined by adding starch solution, although the yellow color which results in the presence of the merest traces of peroxides is easy to distinguish. The presence of peroxides

may then be confirmed by any of the other tests devised by the authors, or by Jorissen's vanadic acid test.

Ether prepared from alcohol denatured with methyl alcohol and pyridin bases often contains methyl ethyl ether and acetone. Frerichs [1] describes tests for detecting these bodies. For the detection of the first named a 250- or 500-mil sample, the boiling-point of which has been ascertained, is distilled and the boiling-point of the first 50 mils noted. If essentially lower than that of the sample the presence of the impurity is indicated, assuming of course that the absence of other usual impurities has been assured. As ordinarily determined the temperature of the boiling-point rises until it shows the boiling-point of pure ether. Frerichs shows an apparatus which can be operated so that the boiling-point may be observed for a long time. One hundred mils of the sample together with a glass capillary sealed at the top to avoid bumping are introduced and



heat applied by insertion of base into an air-bath, the thermometer resting in neck (*A*) so that bulb reaches to *X*. Neck *B* is connected with a reflux. As soon as a steady and vigorous return from *B* is noted the thermometer will indicate a constant boiling-point.

To detect acetone 100 mils of ether are shaken vigorously with 10 mils water. The ether is withdrawn and the aqueous liquid divided into two parts. To one 10 drops sodium nitroprusside solution are added, 6 drops sodium hydroxide, 5 mils water and then acetic acid in slight excess; if the liquid does not completely decolorize and a reddish or violet color appears acetone is indicated. The second portion is then tested with iodine and ammonia and heated until any black precipitate disappears and the liquid becomes clear and bright yellow. A crystalline precipitate of iodoform indicates acetone.

Ether is one of the substances which has to be declared upon the label if it occurs in mixtures intended to be used as drugs. It is classed as a derivative of alcohol. The determination of ether in alcoholic mixtures

[1] Apoth. Zeit., 28, 628.

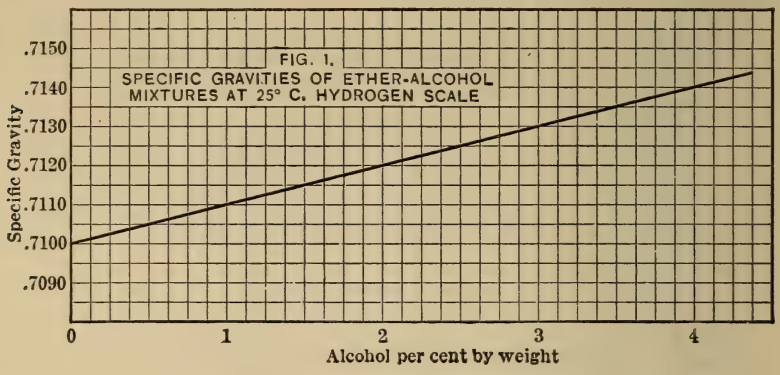
has been described under Alcohol, page 539. With preparations which are more complex than the ordinary alcohol ether mixture, the alcohol and ether should be separated from the other substances by distillation, first diluting the sample with water. The distillation is best accomplished by heating 50–100 mils of the sample in a round-bottom flask, using a direct flame and running the distillate through a long and well-cooled condenser into a receiver surrounded with ice, the neck of which is well over the adapter, and stuffed with absorbent cotton. The distillate can then be transferred to the apparatus used for determining the ether. After the latter has been estimated the alcohol can be estimated in the aqueous portion by distillation.

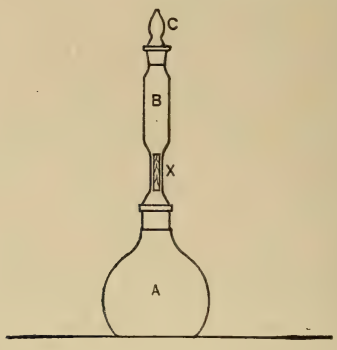
Determination of Small Amounts of Alcohol and Water in Ether. Mallinckrodt and Alt.[1]—The flask used was a 100-mil Regnault pyknometer for taking the density of solids. It is best to have two and make the analysis in duplicate.

Fifteen grams of potassium carbonate dried at 200 to 250° are placed in the bulb *A* and accurately weighed after replacing the stem *B*. Remove the stem and introduce quickly 50 mils of the ether for analysis. Replace stem and allow the flask to stand fourteen hours with frequent shaking. By removing the stopper and holding the inverted flask in the warm hand, the ether can be filtered out through the cotton plug *X*. Care must be used to insure a clear filtrate, otherwise there will be a loss of potassium carbonate. Examine the filtrate after standing to see that no finely divided carbonate has separated out. Fill the upper enlargement *B* with absolute ether and cause it to be drawn in by pouring some of the ether over the bulb. Shake well and expel the ether as before. Wash four times in this manner, which removes the alcohol from the salt. Now dry the flask, with cap *C* removed, at 50° until the carbonate can be shaken down into the flask. Remove the stem and replace it with a drying tube filled with carbonate of potassium to prevent access of external moisture and d y for 1 hour at 50°. Remove the drying tube and after sweeping out the remaining ether vapor with gentle suction for fifteen seconds, replace the stem and cool in a desiccator and weigh. Since it does not require much ether vapor to affect the weight, care is required to secure its complete removal without introducing moisture from an excess of air. A second weighing should be made after drying again for half an hour. The weights should be constant within about 4 mg. The difference between the weights of the potassium carbonate before and after treatment with ether is the weight of water in the sample taken. For the alcohol analysis, treat 100 grams of the sample with 40 grams of freshly dried potassium carbonate for fourteen hours in a glass-stopped flask, shaking frequently. The pyknometer is filled with the clear ether

[1] J. Ind. and Eng. Chem., 1916, 8, 811.

and the specific gravity is determined at exactly 25° on the hydrogen scale. The per cent of alcohol may then be read off from the curve. Obviously if this curve is to be used, the gravity must be made in a bath at exactly 25° on the international hydrogen scale or else a new curve made by the operator at the temperature of his thermostat, which is a simple matter.





ORGANIC PEROXIDES

These substances are related to the metallic peroxides in the same way that ethers are related to the oxides, and alcohols to the hydroxides. They may be considered as hydrogen peroxide in which the hydrogen atoms have been replaced by organic radicles.

$$\begin{matrix} R—O \\ | \\ R—O \end{matrix}$$

There are only two of these substances at present which have attained any commercial importance and which may be encountered in analytical practice, benzoylacetyl peroxide or acetozone and disuccinyl peroxide or alphozone.

These organic peroxides are used as intestinal antiseptics in typhoid and enteric fevers, and also for local infections where they can be brought in contact with the diseased surface such as ulcers, abscesses, inflammation of the mucous membranes, and infectious skin diseases. Acetozone is recommended as an antiseptic in ophthalmic, aural, and nasal practice, and is dispensed in an oil medium with chloretone.

Benzoylacetyl peroxide, $C_6H_5CO \cdot O \cdot O \cdot OCCH_3$

Acetyl-benzoyl peroxide occurs in white, shining crystals, melting at 36.6° C. When heated it slowly decomposes and volatilizes. Water at 25° C. dissolves one part in 1.560 or .639 gram in 1000 mils. It is soluble in oils to the extent of about 3 per cent, slightly soluble in alcohol, and fairly so in ether, chloroform, and carbon tetra-chloride, though all solvents slowly decompose it with the exception of neutral petroleum oils.

In the presence of water it undergoes hydrolysis and slowly decomposes.

As found in the market, acetozone is of a grayish-white color, possessing the properties of the crystalline substance, with the exception that the absorbent powder employed is insoluble.

When dispensed at the bedside the powder is mixed with water and the solution consumed by the patient; but when sold by the druggist on prescription it is often put up in capsules.

Succinic dioxide or Disuccinyl peroxide, $(COOH \cdot CH_2CH_2CO)_2O_2$

It is a fluffy, white, crystalline powder, the crystals being small irregular plates. It dissolves in 30 parts of water at ordinary temperature. It is moderately soluble in alcohol, acetone, and ethyl acetate, sparingly soluble in ether, insoluble in benzene, chloroform and petroleum ether. Odorless or nearly so; softens at 115° C. and melts at 127° C. with decomposition. When brought into a flame it explodes, but it does not explode on percussion or friction. It deteriorates slightly on continued exposure to air, but if kept tightly stoppered and in a dark place it remains unchanged indefinitely.

It is a powerful oxidizing agent, liberating iodin from potassium iodide. It can be identified by its physical properties and its powerful oxidizing action. To test its strength add 2 grams of potassium iodide to 1 gram of alphozone dissolved in 60 mils of distilled water. To this slowly add decinormal solution of sodium thiosulphate with constant agitation until the red-brown color of the iodin is just discharged. Each mil of sodium thiosulphate solution is equivalent to .0117 gram of alphozone; 1 gram of pure alphozone is equivalent to 85.41 mils decinormal sodium thiosulphate solution.

CHAPTER XVI

ALDEHYDES AND KETONES

ALDEHYDES

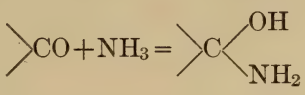
This class of organic bodies includes the two very important medicinal agents, formaldehyde and chloral. The aldehydes are derived from the primary alcohols by the removal of two atoms of hydrogen from the $—CH_2OH$ group, thus methyl alcohol on mild oxidation gives formaldehyde. They are named after the fatty acids which they yield on oxidation.

With the exception of the gaseous body formaldehyde, whose physical properties are unknown, the lower members of the aldehyde series are colorless, mobile, neutral, volatile liquids, soluble in water, though the solublity decreases as the number of carbon atoms increases. The higher aldehydes are usually waxy solids, insoluble or nearly so in water but readily soluble in alcohol and ether. They are closely related to the ketones because they are similar in constitution, both classes containing the carbonyl group $=CO$. The lower members form crystalline addition compounds with sodium bisulphite, which are soluble in water, but insoluble in alcohol and ether, and are decomposed on warming with acids or alkalies with regeneration of the aldehyde. They form oximes with hydrohydroxylamine, and hydrazones or phenylhydrazones with phenylhydrazine, a molecule of water being split off in the reaction. Both oximes and hydrazones are usually decomposed by hot concentrated hydrochloric acid with regeneration of the aldehyde.

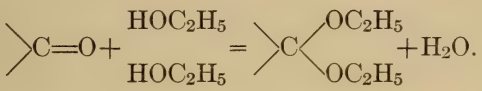
Aldehydes on reduction with nascent hydrogen yield primary alcohols. With phosphorus pentachloride they give dihalogen derivatives of the paraffins, the oxygen of the $=CO$ group being displaced by two atoms of chloride. Acetaldehyde gives dichlorethane, called ethylidene chloride, because it contains the ethylidene group, $CH_3 \cdot CH \cdot CH_3CHO + PCl_5 = CH_3CHCl_2 + POCl_3$. Aldehydes combine directly with hydrocyanic acid to form hydroxycyanides,

$$\rangle CO + HCN = \rangle C \begin{matrix} OH \\ CN \end{matrix}$$

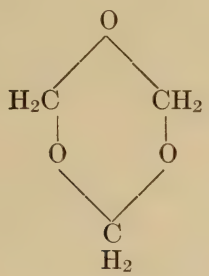
Aldehydes possess a number of characteristic properties which differ essentially from the ketones. On exposure to the air they are quite easily converted to fatty acids, they are readily oxidized by an ammoniacal solution of silver oxide, forming a silver mirror, and reduce Fehling's solution. They form addition products with ammonia



which are usually crystalline, soluble in water, and yield the aldehyde again on treatment with dilute acids. They combine with two molecules of alcohols to produce acetals,



They are unstable in presence of alkalies, by which thay are converted to brown resins. Aldehydes undergo polymerization which may take place spontaneously, but usually on the addition of some substance such as zinc chloride or sulphur dioxide. The common form of polymerization is the combination of three molecules of the aldehyde to form paraldehydes such as paraformaldehyde or trioxymethylene and paracetaldehyde often called simply paraldehyde. The constitution of these polymers are usually represented as follows:



Paraformaldehyde

They are decomposed into the original aldehydes on distillation with dilute mineral acids. They do not show the characteristic reactions of aldehydes and do not contain a $\rangle CO$ group.

Formaldehyde is an excellent deodorant and disinfectant, but is too irritating for general medicinal use. As a disinfectant it has quite taken

the place of sulphur and it is almost universally used in embalming fluids. It is also valuable as an insecticide and a sweetened solution of commercial formaldehyde is a valuable agent for destroying the common housefly.

In small amounts formaldehyde will sometimes be found in tooth pastes, washes, gargles, whooping cough inhalants, and eye lotions, and in fluid preparations recommended as deodorants. Paraformaldehyde or trioxymethylene is sold in tablet form as a remedy for hoarseness and sore throat and also for diarrhea, as it is somewhat astringent. It is dispensed in collodion in wart remedies and the vapors of the pure substance are recommended for consumptives and as an ingredient of surgical bandages and dressings. During the last decade a number of true and pseudo derivatives and compounds of formaldehyde have appeared on the market and will be discussed subsequently.

Hexamethyleneamine is probably the most important derivative of formaldehyde medicinally, and is used as an antiseptic for the genito-urinary tract in all infectious diseases common to that locality, also as a urinary disinfectant in typhoid and for aborting coryza and acute conditions of the nasal passages.

Formaldehyde, HCHO

Formaldehyde or methaldehyde is known only in dilute solution and in the form of a gas at high temperatures. It would probably be a gas at ordinary temperature. The aqueous solution of formadehyde has a very penetrating, suffocating odor and a neutral reaction. It is a powerful reducing agent and readily undergoes oxidation, producing formic acid; and when treated with reducing agents it is converted to methyl alcohol. It reduces ammoniacal silver oxide, combines directly with sodium bisulphite, and forms formaldoxime with hydroxylamine, which readily undergoes polymerization.

When an aqueous solution of formaldehyde is evaporated paraformaldehyde resu ts. The latter is a colorless amorphous substance, subliming readily and melting 171°. When strongly heated it is completely decomposed into pure gaseous formaldehyde, but as the gas cools paraformaldehyde again results. When heated with a large amount of water it is reconverted into formaldehyde.

Formaldehyde forms several polymeric modifications. When its aqueous solution is treated with lime water or other weak alkali formose results which is a mixture of substances belonging to the sugar group.

The aqueous solution of formaldehyde containing not less than 37 per cent of the gas is recognized in the Pharmacopœia.

Compositions for generating formaldehyde vapors consist of the solid substance or a solution mixed with permanganates or alkali peroxides or bisulphites. The general idea is that formaldehyde is held by the alkali or bisulphite and on the addition of permanganate in aqueous solution the gas is liberated. In solid products the permanganate or peroxide is included and simple addition of water liberates the formaldehyde. The oxidation of formaldehyde in soap solutions is prevented by the addition of sulphite.

The identity tests given by formaldehyde are very striking, and are performed with an aqueous solution of the substance. The bright rose color given with sulphuric acid and resorcin has been described in detail under Methyl Alcohol page, 531. The morphin test may be carried out by adding a few drops of the suspected liquid to 5 mils sulphuric acid, cooling and pouring a little of the liquid on some morphin crystals on a white porcelain surface, when a deep purple color will be produced.

Mullikin's beta-naphthol test is carried out by mixing a small quantity of the solution under examination with dilute alcohol 1–2 and adding about .005 gram beta-naphthol, 3 to 5 drops of hydrochloric acid and boiling. The precipitate is collected on a filter, washed with alcohol 1–2, and recrystallized out of boiling alcohol. The methylenedibetanaphthol formed melts 189°.

A modification of the morphin test suggested by Bonnel directs that the surface of a dish or watch-glass should be moistened with sulphuric acid containing a trace of morphin and exposed to the vapors rising from the sample under investigation. If formaldehyde is present in the vapors the characteristic purple shade will be developed.

The analyst will often be called upon to determine the strength of formaldehyde solutions for sale on the market.

The hydrogen peroxide method is official in the Pharmacopœia.

Transfer 3 mils of Solution of Formaldehyde to a tared flask containing 10 mils of distilled water, tightly stopper and weigh accurately. Add to the contents of the flask 50 mils of normal potassium hydroxide V. S., and follow this immediately but slowly through a small funnel with 50 mils of solution of hydrogen dioxide which has previously been rendered neutral to litmus with potassium hydroxide. Now heat the mixture cautiously on a water-bath for five minutes, shaking occasionally during this time; allow the mixture to cool, rinse the funnel and sides of the flask with distilled water and, after allowing it to stand thirty minutes, titrate with normal sulphuric acid V. S., using litmus T S. as indicator. It shows not less than 37 per cent of CH_2O, correction being made for free acid if present.

Each mil of normal potassium hydroxide V. S. corresponds to .03002

gram of CH_2O. Each gram of solution of Formaldehyde corresponds to not less than 12.3 mils of normal potassium hydroxide V. S.

The writer has found that very good results can be obtained by the iodine method. For this purpose an approximate N/5 Iodin is used, the exact titer of which need not be known because it is advisable to run a blank at the same time. The thiosulphate should of course be accurately standardized. Twenty mils of the solution accurately measured are introduced into a 500-mil graduated flask and made up to the mark with distilled water. Five mils of this solution, measured with a pipette, are placed in a glass-stoppered bottle, 30 mils N/1 sodium hydroxide added, and then with constant agitation the iodin solution is added from a burette, noting the amount, until the mixture appears bright yellow. After shaking for a minute 40 mils of N/1 sulphuric acid is added and the excess of iodin determined by titrating with N/10 thiosulphate. A blank is then run using the same quantities of alkali, iodin, and acid, the difference showing the amount of iodin consumed by the formaldehyde. One mil N/10 iodin is equivalent to .0015 gram formaldehyde. In calculating the percentage by weight the result must be divided by the specific gravity of the formaldehyde solution used.

Formaldehyde can be determined in soap solutions by precipitating the fatty acids with sulphuric acid, filtering, and determining the formaldehyde in the filtrate by the iodin method, the iodin being added before the alkali is introduced. After rendering alkaline the requisite N/1 sulphuric acid is added and the excess of iodine determined by thiosulphate.

Colorimetric Method. Collins and Hanzlik.[1]—Aliquot portions of the formaldehyde solution are measured into Nessler tubes, 2 mils of phloroglucinol reagent (.1 gram of phloroglucinol dissolved in 10 mils of 10 per cent sodium hydroxide solution) is added to each, and the mixtures are diluted to 50 mils. After three minutes, the colorations obtained are compared with standard colors. The latter are prepared from definite quantities of Congo red solution (0.025 per cent in water containing 5 per cent of alcohol) and methyl orange solution (.01 per cent in water); 2.5 mils of the Congo red solution diluted to 50 mils gives the same coloration as 50 mils of .001 per cent formaldehyde solution when both are viewed in a column 12 cm. in depth. Different samples of Congo red do not always give the same depth of color, and the solution should be standardized against potassium bichromate; 2.5 mils of the .025 per cent Congo red solution diluted to 50 mils should have the same tint as a mixture of 1.7616 grams of potassium bichromate and 11.5537 grams of sulphuric acid diluted to 50 mils. The addition of methyl orange solution to the standards is necessary only when dealing with low concentrations of formaldehyde. The proportions of Congo red and methyl orange corresponding with different con-

[1] J. Biol. Chem. 1916, 25, 231.

centrations of formaldehyde are given in the following table, the mixtures being diluted to 50 mils and viewed in a 12-cm. column:

Formaldehyde Per Cent	Congo red (0.025 per cent solution) Mils	Methyl Orange (0.01 per cent solution) Mil	Formaldehyde Per Cent	Congo red (0.025 per cent solution) Mils	Methyl Orange (0.01 per cent solution) Mil
0.005	20.0	0	0.001	2.5	0
0.0033	11.0	0	0.0005	0.85	0.4
0.0025	9.0	0	0.0040	0.65	0.35
0.002	8.0	0	0.0002	0.23	0.18
0.0016	5.0	0	0.00014	0.20	0.15
0.00125	4.0	0	0.0001	0.13	0.10

To determine formaldehyde in urine, the phosphates present must be removed by treatment with sodium hydroxide solution and filtration before the above method is applied. Experiments with known quantities of formaldehyde showed that the method was more accurate than several other methods with which it was compared. The chlorimetric method may be used to determine hexamethylenetetramine in urine, etc., the latter is distilled without the addition of acid and the process applied to the distillate. If formaldehyde is also present in the urine, this must be determined previously and its quantity deducted from the total amount.

Paraformaldehyde and Trioxymethylene

The valuable properties of formaldehyde and the inconvenience of handling an aqueous solution soon created a demand for a solid form of the substance, and it is now marketed to a large extent in the polymerized condition.

There is a confusion in some minds regarding the terms paraformaldehyde and trioxymethylene, they are often used synonymously and with good reason, since their formation is so nearly identical, and for the information of the workers in this field who may be involved in legal quibbles concerning these points reference will be made here to the work of Auerback and H. Barscall,[1] whose work on the polymers of formaldehyde may be summarized as follows:

Paraformaldehyde is an amorphous colloidal substance with a molecular weight at least three times that of formaldehyde, and containing a variable quantity of absorbed water. When prepared by concentrating solutions of pure formaldehyde, it melts at about 150–160° C., dissolves

[1] Arbb. Kais. Gesundt. Amt., 1907, 27, 183; Jour. Soc. Chem. Ind., 1907, 1294.

to the extent of 20 to 30 per cent in water at 18° C., is insoluble in ether and alcohol, is not altered by boiling with water, and forms an addition-compound with sodium sulphite. α-Polyoxymethylene, $(CH_2O)n$, is obtained by the addition of 1 volume of concentrated sulphuric acid to 10 volumes of a pure aqueous solution of formaldehyde. It forms ill-defined crystals which melt at 163–168° C. when heated in a sealed tube, but are volatilized without melting when heated in an open tube. It is soluble to the extent of 11 per cent in water at 18–25° C., is insoluble in alcohol and ether, and forms a compound with sodium sulphite. Its vapors at 189° C. are composed of single CH_2O-mols. β-Polyoxymethylene is precipitated from a pure aqueous solution of formaldehyde by addition of .4 volume of concentrated sulphuric acid. It is crystalline, melts at 163–168° C. when heated in a sealed tube, is soluble to the extent of 3.3 per cent in water at 18° C., and up to 4 per cent in water at 25° C., and is insoluble in alcohol and ether. Its vapor density is 32 at 184° C. and increases slowly with rising temperature. It forms a compound with sodium sulphite, and when heated at 100° C. is converted into the γ-modification. γ-Polyoxymethylene—On addition of .4 volume of sulphuric acid to formaline (a solution of formaldehyde containing methyl alcohol), γ-polyoxymethylene is precipitated along with the corresponding β-compound, and is freed from the latter by treatment with sodium sulphite solution. It is distinctly crystalline and melts at 163–165° C. It dissolves in water at 18–25° C. to the extent of about .1 gram in 100 mils, and is insoluble in alcohol and ether. It does not react with sodium sulphite. At 184 and 198° C., its vapors contain polymerized molecules together with simple CH_2O-mols.; the proportion of the former increases with rising pressure and decreases with rising temperature, the vapor densities at the temperatures given are 40 and 60 respectively. On boiling with water, γ-polyoxymethylene is converted into the δ-modification. δ-Polyoxymethylene, obtained by prolonged boiling of the γ-compound with water, forms ill-defined crystals, the melting-point (169–170° C. in a sealed tube) of which is lowered by even traces of impurities. This modification also melts when heated in an open tube, whereas all of the others are volatilized below the melting-point. It is insoluble in alcohol and ether and nearly so in water. Its vapor density slowly decreases between 190 and 240° C.; at these temperatures the vapors consist of highly polymerized molecules which split up only very slowly into simpler ones. The compound does not react with sodium sulphite. α-Trioxymethylene, $C_3H_6O_3$, is formed by sublimimg polyoxymethylene and collecting the sublimate in water. Commercial "trioxymethylene" (β+γ-polyoxymethylene, or γ-polyoxymethylene) was sublimed by heating in a glass retort in a slow current of nitrogen, and the sublimate was collected in a receiver containing a small quantity of water, and cooled

by ice. The distillate was submitted to fractional distillation, and the crystals which separated from the earlier fractions were purified by recrystallization from ether, or by sublimation in closed tubes.

α-Trioxymethylene obtained in this way forms colorless needles or strongly refracting prisms, which are tough and soft, and melt at 63–64° when heated in closed tube. It boils at 114.5° C. at 759 mm., but is very volatile even at the ordinary temperature. It is soluble to the extent of 17.2 grams in 100 mils of water at 18° and 21.1 grams in 100 mils at 25° C.; it is easily soluble in alcohol, ether, methyl alcohol, acetone, chloroform, carbon tetrachloride, carbon bisulphide, and benzene, and soluble with difficulty in petroleum ether. It is probably a cyclic compound, as unlike the other polyoxymethylenes, it does not respond to the usual reactions for aldehydes or ketones; with sodium sulphite it does not react either in alkaline or acid solution. It exhibits a constant vapor pressure and vapor density.

Paraformaldehyde differs from α-polyoxymethylene chiefly by its amorphous condition and its content of adsorbed water, and by the properties depending upon these factors. Paraformaldehyde and α, β, γ and δ polyoxymethylenes all exhibit a tendency, decreasing in the order given, to split off formaldehyde as a gas or in aqueous solution; the aqueous solutions of these compounds do not differ from those of formaldehyde.

Paraformaldehyde or trioxymethylene with formamide or acetamide gives compounds of the type $R : NHCH_2OH$, used as antiseptics and uric acid solvents.

E. Rust [1] has modified the hydrogen peroxide method in such a way as to render it available for the determination of formaldehyde in tablets and pastiles containing trioxymethylene. A funnel is placed in the mouth of a 250-mil conical flask, and 19–20 grams of the powdered substance weighed into it from a tube. The substance is washed down into the flask with 70 mils of N/1 sodium hydroxide delivered from a burette and dissolved. Then 9–10 grams of neutral 30 per cent hydrogen peroxide are added at first in small portions and cautiously so as to avoid heating and filtering, and then more rapidly. After two hours the contents of the flask are heated cautiously to boiling and boiled to destroy the excess of peroxide. The funnel is now rinsed into the flask, a drop or two of phenolphthalein added and the liquid titrated with N/1 acid to very slight excess and then titrated back with N/1 alkali. Any required acidity or alkalinity of the substance must be tested for and if found titrated and allowed for.

[1] Z. angew. Chem., 1906, 19, 138.

FORMALDEHYDE DERIVATIVES AND COMPOUNDS

There have appeared on the market a number of compounds of formaldehyde with various substances, among which may be mentioned condensation products with nucleinic acids, tannins, and tannin-like substances or their derivatives which claim antiseptic and astringent properties without the irritating effects of the formaldehyde, phenols, carbo-hydrates, starch, malt-extract, etc. Many of these are patented and sold with great claims for their therapeutic effects, and while some are true compounds, others are simply mixtures probably holding the formaldehyde in absorption, or as the polymerized form from which the gas is regenerated under suitable conditions. These uncertain substances may furnish material for endless controversy in patent litigation and therapeutical opinion.

Methylal

Methylal, $CH_2(OCH_3)_2$, may be obtained by boiling aqueous formaldehyde with methyl alcohol and a little sulphuric acid, but it is usually prepared by oxidizing methyl alcohol with manganese dioxide and sulphuric acid. It is a pleasant-smelling liquid, specific gravity .855 at 15° C., boiling 42°, readily soluble in water, alcohol, and oils, and when distilled with sulphuric acid is resolved into methyl alcohol and formaldehyde. It is used as a soporific administered in syrup or water, also injected in 10 per cent solution, and is used locally in liniments or ointments as a local anesthetic.

Amyloform

A condensation product of formaldehyde and starch, white, odorless powder, insoluble in ordinary solvents and possessing antiseptic properties. It is used as a substitute for iodoform.

Formaldehyde Acetate

Methylene diacetate, $CH_2(C_2H_3O_2)_2$, is a heavy colorless liquid, boiling 170° C., soluble in alcohol and in water with decomposition. It has antiseptic properties. It is prepared by the action of methylene iodide on silver acetate.

Glutol-Schleich

Glutol-Schleich or Formalin Gelatin, is a chemical combination of gelatin and formaldehyde.

It is a white odorless powder, insoluble in water under ordinary conditions, but dissolved when heated with water under pressure, the solu-

tion thus produced gelatinizing on cooling. It is not changed by the action of acids, but is slowly decomposed in contact with living cells.

It is to be used as an antiseptic dressing.

Formicin

Formicin is formaldehyde-acetamide, $CH_3 \cdot C \cdot O \cdot NH \cdot CH_2 \cdot OH$, a molecular compound of formaldehyde and acetamide.

It is a slightly yellowish, thick, syrupy liquid, having a faint, formaldehyde-like odor and a slightly acid, bitter taste. The specific gravity should be between 1.14 and 1.18 at 20° C. Formicin is soluble in water, alcohol, chloroform, and glycerin; it is nearly insoluble in ether. An aqueous solution (1 to 10) has an acid reaction on litmus.

At 115° C. to 120° C. formicin dissociates. If 1 mil of an aqueous solution of formicin (1 to 10) is mixed with 1 mil of a mixture composed of equal volumes of stronger ammonia water, potassium hydroxide test solution and silver nitrate test solution, no immediate darkening should take place; but if the mixture is allowed to stand for some time, or is warmed, darkening occurs, due to the separation of metallic silver.

Solutions of formicin liberate formaldehyde gradually at body temperature, and thus exert an antiseptic action.

Fortoin—Methylene-Dicotoin

Fortoin, $CH_2(C_{14}H_{11}O_4)_2$, is a condensation product of cotoin and formaldehyde.

Fortoin forms yellow, needle-shaped, tasteless crystals, melting at 211° to 213° C. It is insoluble in water, sparingly soluble in alcohol, ether, or benzol, but freely soluble in dilute alkalies, acetone, or chloroform. It dissolves in cold concentrated sulphuric acid with an orange color, and on warming the solution becomes ruby red.

It is used as an antidiarrheic in acute and chronic intestinal catarrh and in obstinate diarrheas.

Formaloin

This product is a yellow, amorphous, tasteless powder soluble in alkalies, with difficulty in alcohol and insoluble in water. It is a condensation product of formaldehyde and aloin and it is used for the same purposes as aloin.

Forman

This is a colorless, unstable oily liquid, readily decomposed by water or moist air, prepared by the action of formaldehyde on menthol in the presence of hydrochloric acid gas. Chemically it is chlormethylmenthyl

ester, $C_{10}H_{19}OCH_2 \cdot Cl$. It is soluble in oils and is used in catarrhal affections either as an inhalant or on absorbent cotton.

Formopyrin

Methylenediantipyrin, $(C_{11}H_{11}N_2O)_2 = CH_2$, prepared with formaldehyde and antipyrin, forms colorless crystals, melting 176–177°, soluble in alcohol and almost insoluble in water.

Ichthoform

This product is prepared from formaldehyde and ichthyol, and is a dark-brown, practically odorless and tasteless powder, permanent and generally insoluble.

Empyroform

Empyroform is a condensation of birch tar and formaldehyde.

According to the patent specifications birch tar is boiled with formaldehyde solution and the hot liquid poured into hydrochloric acid. When cold, the solid mass is collected and washed until free from acid.

It is a grayish-brown, almost odorless powder, insoluble in water, but soluble in acetone and chloroform.

Empyroform is an antipruritic, sedative, and desiccant.

Soap solutions containing formaldehyde are marketed under the name "Veroform."

Resorcinoform

This product results from the reaction of resorcinol and formaldehyde in the presence of hydrochloric acid, and is an amorphous currant-red powder with antiseptic properties.

Hexamethylenetetramine, $(CH_2)_6N_4$

This body should strictly be taken up with the amines, but it is more conveniently discussed at this point as it is a derivative of formaldehyde. It results from the reaction of ammonia with formaldehyde.

$$6CHOH + 4NH_3 = (CH_2)_6N + 6H_2O$$

It is official in our Pharmacopœia, and is sold under its chemical name and by a number of trade names associated with the firms exploiting it including aminoform, cystamin, cystogen, formin, uritone, urotropin, etc.

It occurs in the form of colorless, lustrous, odorless crystals, readily soluble in water and alcohol and slightly in ether. The aqueous solution

is alkaline. It sublimes at 263° C. without melting and with partial decomposition. It is precipitated by Mayer's reagent, mercuric chloride, tannin, bromin, and other alkaloidal reagents. Bromin produces a brick-red precipitate, $C_6H_{12}N_4Br_4$, which on drying becomes yellow and is converted to the dibromide melting slightly below 200° C.

One-tenth gram of the solid substance with .1 gram salicylic acid and 5 mils sulphuric acid gives a carmine-red color on warming.

In the general scheme of qualitative analysis this body will remain in the aqueous solution through both of the acid and alkaline shake-outs. If a small portion of the solution which has been subjected to the regular treatment, is removed and acidulated, and if still found to give a marked precipitate with Mayer's reagent, the presence of hexamethylenetetramine may be suspected The solution should then be made strongly alkaline with sodium hydroxide and boiled until all the ammonia is dispelled, the hexamethylenetetramine being unaffected; it is then made acid with sulphuric acid and boiled again, preferably first under a reflux and then partly distilled, the distillate being tested for formaldehyde. The acid liquor is then treated with an excess of sodium hydroxide and boiled and if ammonia is now obtained the presence of the compound suspected is established.

Puckner and Hilpert [1] use this method for estimating the substance. The liquid is first boiled with strong caustic alkali by which it is unaffected until all the liberated ammonia is driven off, then boiled with acid and finally with alkali, collecting the distillate in a known amount of standard acid and titrating back with alkali as in a Kjeldahl nitrogen determination.

Hexamethylenetetramine may also be determined by precipitating it from acetic acid solution by mercuric chloride which yields the compound, $C_6H_{12}N_4 \cdot 2HgCl_2$, this is washed with water containing mercuric chloride, dissolved in concentrated sodium chloride solution, the mercury precipitated by potassium hydroxide, filtered, the filtrate acidulated with sulphuric acid and the regular Kjeldahl combustion and distillation prosecuted. This method has been advanced by Schroter [2] for determining the body in urine.

EVALUATION OF HEXAMETHYLENETETRAMINE TABLETS. W. O EMERY

Reagents:

A. Modified Nessler's Reagent, involving:

(*a*) Solution of 10 grams $HgCl_2$, 30 grams KI and 5 grams acacia in 200 mils water, filtered through a pledget of cotton, and

(*b*) Solution of 15 grams NaOH in 100 mils water.

[1] J. Amer. Chem. Soc., 1908, 30, 1471. [2] Arch. exp. Path. Pharm., 64, 161.

B. Tenth normal iodin.

C. Twentieth normal thiosulphate.

Ascertain the weight of 20 or more tablets, triturate in a mortar to a fine powder and keep in a small capsule tightly closed with a cork or glass stopper. Weigh out .5 gram of the powdered product on a metal scoop or watch-glass, transfer with sufficient water to a round-bottom flask, add additional water to a total volume of 100 mils and finally 25 mils 10 per cent HCl. Connect with a reflux condenser (preferably of the worm type) and boil gently fifteen minutes, then after cooling wash-out condenser tube with a little distilled water and transfer contents of flask quantitatively to a graduated 250-mil flask, finally diluting to the mark with water.

With a pipette withdraw 10 mils (containing in the case of a pure product the elements of .02 grams $C_6H_{12}N_4$) of the solution so prepared to a 200-mil Erlenmeyer containing a mixture (chilled in ice water if available) of 20 mils reagent *A* (*a*) and 10 mils reagent *A* (*b*), wash down neck of container with a jet of water from the wash bottle and allow to stand at least one minute. Now add 10 mils 40 per cent acetic acid in such manner that the inside of neck is completely washed by the reagent, mix quickly and thoroughly by rotating and tilting flask, and immediately run in from a burette 20 mils of *B*, then titrate with *C* (adding 5–10 drops starch solution toward the end of the operation) to the disappearance of the blue coloration. The final color of the solution is a pale straw-green. If preferred, the end-point may be determined on the reappearance of a faint blue coloration, induced by the addition of further iodin.

The reaction taking place between formaldehyde and potassium mercuric iodide in the presence of caustic alkali is given in the equation:

$$CH_2O+K_2HgI_4+3KOH=Hg+HCO_2K+4KI+2H_2O$$

In carrying out the method proper, unusual care is necessary in adding and mixing the several reagents with the preceding menstruum so that uniform solution shall result. This is effected by judicious rotation and tilting of flask, and at certain points also by washing down the neck of container with a jet of water. Addition of iodin should follow acidification with the greatest possible dispatch, on account of the fact that long standing of the mixture in the presence of free acetic acid invariably leads to low values for hexamethylenetetramine, due apparently to partial solution of colloidal mercury. The primary chilling of Nessler's reagent is advocated in order to minimize to the utmost any tendency toward secondary reactions, as also to avoid possible loss of iodin through undue increase in temperature on acidifying with acetic acid.

Since the standard iodin (reagent *B*), employed has twice the strength of the thiosulphate (reagent *C*), and 1 mil tenth normal iodin is equivalent

to .001167 gram hexamethylenetetramine, the quantity of this product in the aliquot under examination is readily calculated from the expression:

$$\frac{H-I}{2} N\ 0.001167$$

in which H = number of mils reagent C equivalent to 20 mils reagent B, I = number mils reagent C required to offset the unexpended iodin, and N = normality of reagent B.

Derivatives and Compounds of Hexamethylenetetramine

There are many substances on the market claiming to be derivatives of hexamethylenetetramine, some of which are protected by patent. Some of these are claimed to be compounds with boric, citric, and other acids, with guaiacol and various phenols, with acid salts, sulphonic acid, etc. With certain compounds, simple treatment with chloroform is sufficient to remove the hexamethylenetetramine unchanged, and it is evident that the claim of possessing a new body is in some cases entirely unfounded.

It is claimed that stable solutions of mercury and hexamethylenetetramine can be obtained by mixing the mercuric compound with a soluble albumin or the sodium salt of casein or an albuminate, and stirring into a large excess of 5 per cent soap solution.

Hetralin

Resorcinol-hexamethylenetetramine forms white crystalline needles, soluble in alcohol and water and decomposing above 160°. It is recommended as a diuretic and used in gonorrheal affections.

Hexal

Hexal is hexamethyleneamine salicylsulphonic acid,

$$(CH_2)_6N_4 \cdot C_6H_3(OH)COOH \cdot HSO_3.$$

It is a white, odorless, crystalline powder, readily soluble in water, slightly soluble in alcohol and difficultly soluble in ether, having an acid taste.

A dilute aqueous solution of hexal gives a violet color with ferric chloride, a white precipitate with aqueous albumin solution, and an orange-colored precipitate with bromin water.

With the exception of the tannic acid test, hexal responds to the identity tests of the U. S. Pharmacopœia for hexamethylenemine.

If .1 to .2 gram hexal is moderately heated with 5 mils concentrated sulphuric acid, a carmine-red color will be produced.

Hexal is claimed to be useful in chronic inflammations of the bladder and in urethritis.

Hexamethylenamine Methylenecitrate—Helmitol

Hexamethylenamine methylenecitrate, $C_6H_8O_7(CH_2)_6N_4$, is a compound of hexamethylenamine with anhydromethylenecitric acid.

It is a white, crystalline powder, melting with decomposition at 165 to 175° C., having an agreeable, acidulous taste and acid reaction. It is soluble in about 10 parts of water, but almost insoluble in alcohol and ether. By dilute acids and more easily by alkalies it is decomposed with the liberation of formaldehyde. On addition of 1 per cent solution of phloroglucin to a solution of hexamethylenamine methylenecitrate, followed by sodium hydroxide, the intense rose-red color characteristic of the liberated formaldehyde is developed.

It is used in cystitis, pyelitis, prostatic diseases, and urethritis.

Saliformin

Hexamethylenamine salicylate, $(CH_2)_6N_4C_6H_4 \cdot OH \cdot COOH$, is a weak salt of hexamethylenamine and salicylic acid.

It is a white, crystalline powder, having an acidulous and disagreeable taste, readily soluble in water or alcohol.

It is soluble in cold sulphuric acid without color, becoming crimson on heating. Its aqueous solution is colored deep green by copper sulphate, violet by ferric chloride, and forms a yellow precipitate with bromin.

It is decomposed with basic substances (soluble hydroxides, carbonates, etc.) and by strong acids. It is incompatible with salts of iron and other metals which form insoluble compounds with salicylates.

It is said to be useful in cystitis, lithiasis, and bacterial affections of the urinary passages, also in gout, etc.

Tannopin—Hexamethylen-tetramine Tannin—Tannon

Tannopin, $(C_{14}H_{10}O_9)_3 \cdot (CH_2)_6N_4$, is a condensation product of tannin with hexamethylenamine.

It is a fine, fawn-colored and tasteless, nonhygroscopic powder, containing 87 per cent of tannin and 13 per cent of hexamethylenamine. It is insoluble in water, weak acids, alcohol, chloroform, or ether, but slowly soluble in dilute alkalies. On heating dry tannopin, it swells and gives off the odor of formaldehyde. The odor of formaldehyde is also developed on heating tannopin with dilute sulphuric or hydrochloric acid, while on boiling with sodium hydroxide solution it splits off ammonia. The clear aqueous filtrate from tannopin does not give a reaction with ferric chloride.

Tannopin has an astringent and antiseptic action in the intestine; it passes unchanged through the stomach, but being gradually decomposed by alkalies, it becomes effective in the intestinal tract, exerting the action of its two components.

Urystamine is probably a mixture of lithium benzoate and hexamethylenetetramine.

Thial

Hexamethylenamine oxymethylsulphonate is a white odorless powder, easily soluble in water and used as an antiseptic.

Bromalin

Hexamethylenetetramine bromethylate, $C_6H_{12}N_4C_2H_5Br$. Forms colorless crystals, melting 200°, soluble in water and used as a nerve sedative. It is claimed that it causes no brominism.

Iodoformin

Iodoformin is claimed to be a compound of hexamethylenamine and iodoform containing 75 per cent of iodoform. It is insoluble in water and is used for the same purposes as iodoform.

Iodoformal, $C_6H_{12}NC_2H_6ICH_3I$

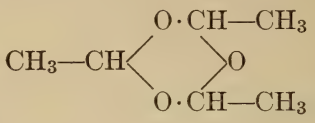
Iodoformal is obtained by the action of ethyl iodide on iodoformin. It is lemon-yellow odorless powder insoluble in water.

ACETALDEHYDE, CH_3CHO

Acetaldehyde is a colorless, mobile, volatile liquid, specific gravity .790 at 15°, boiling 20–21°. It has a peculiar penetrating and suffocating odor, and mixes with water, alcohol, and ether in all proportions. It is slowly oxidized to acetic acid on exposure to air, has powerful reducing properties, and on treatment with reducing agents is converted to ethyl alcohol. With hydroxylamine it forms a crystalline oxime, and when shaken with a concentrated solution of sodium bisulphite, the crystalline addition product separates. It combines directly with dry ammonia, producing a colorless crystalline substance aldehyde ammonia, which is decomposed by acids. When warmed with caustic alkalies it is converted into a brown substance called aldehyde resin.

Three well-defined polymerides are known—aldol, paraldehyde, and metaldehyde. Aldol, $CH_3CH(OH)CH_2CHO$, is produced by the action of dilute hydrochloric acid or zinc chloride at ordinary temperatures. It is a colorless, odorless liquid, miscible with water, and shows all the ordi-

nary properties of an aldehyde. It can be distilled unchanged under reduced pressure, but when distilled under ordinary pressure, or when treated with dehydrating agents it is converted into water and crotonaldehyde, $CH_3 \cdot CH = CH \cdot CHO$. Paraldehyde, $(C_2H_4O)_3$, results when a drop of concentrated sulphuric acid is added to acetaldehyde. It is a colorless, pleasant-smelling liquid, specific gravity .995–.998 at 15°, boiling 121–125° and solidifying in the cold. It is soluble in water, alcohol, ether, chloroform, and oils. It shows none of the ordinary properties of an aldehyde and its construction may be represented by the formula:



It is used as a stimulant, hypnotic, and antispasmodic, being employed for insomnia, and as an antidote for morphin poisoning. It is sometimes dispensed mixed with a fixed edible oil.

Metaldehyde, $(C_2H_4O)n$, is produced by the action of acids at low temperatures. It crystallizes in colorless needles insoluble in water, is sublimable without change, but on prolonged heating or by distilling with acids it is converted into acetaldehyde.

S. S. Sadtler [1] has proposed a method for determining aldehydes based on the reaction with sodium sulphite whereby sodium hydroxide is liberated and titrated. For the determination of citral in lemon oil, from 5 to 10 grams of the sample are made neutral if necessary, treated with 25 to 50 mils of 20 per cent solution of sodium sulphite and neutralized with N/2 hydrochloric acid, using rosolic acid. The red color due to the free alkali is discharged by the acid, and the mixture kept hot and well agitated the titration with acid being continued as long as the color is reformed. The reaction is complete in one-half hour.

$$C_9H_{15}COH + 2H_2O + 2Na_2SO_3 = C_9H_{17}COH(NaSO_3)_2 + 2NaOH$$

The reaction is available for the determination of vanillin, piperonal, and other aldehydes. The phenolic hydroxyl of the vanillin is neutralized by alkali, using rosolic acid, then sodium sulphite added and the titration with acid performed in the hot solution. The alkalinity of the sulphite must be determined and allowed for. Sadtler states that the reaction is complete and immediate with the fatty aldehydes. It will detect minute quantities of formaldehyde and is of value in detecting acetaldehyde in grain alcohol, and acetone in methyl alcohol. This procedure can be used for the determining acetaldehyde in the presence

[1] J. Frank. Inst., 1904, 157, 231.

of paraldehyde, first neutralizing the latter. Richter [1] has worked out the details which are as follows: Ten grams are shaken with 100 mils water, phenolphthalein added, and then N/1 potassium hydroxide until a pink color is obtained; 20 mils of sulphite solution (25 grams—100 mils) are added and the liquid titrated with N/1 hydrochloric acid. A blank is run with 100 mils water and 20 mils of the reagent. Richter says that good commercial specimens of paraldehyde show less than 1 per cent of acetaldehyde, and if kept in full-stoppered bottles away from the light there is no need of any serious contamination.

CHLORAL AND CHLORAL HYDRATE

Chloral, CCl_3CHO, is by far the most important derivative of acetaldehyde from a medicinal point of view, and consequently to the analyst in this field.

Chloral is not prepared by the direct action of chlorine on acetaldehyde, but is made from alcohol. The reaction is complicated, but chloral alcoholate is formed $C \cdot Cl_3 \cdot CH(OC_2H_5)(OH)$, and on distilling this with sulphuric acid, chloral is obtained. It is purified by conversion to the hydrate and on distilling again with acid, the pure chloral results. Chloral with an equivalent amount of absolute alcohol gives chloral alcoholate, melting 48°, boiling 113–114°.

It is a heavy, oily-liquid, specific gravity 1.50, boiling 95–97°, with a penetrating and irritating odor, insoluble in water, but uniting with it. In chemical properties it closely resembles acetaldehyde, having strong reducing properties, and combining directly with ammonia, sodium bisulphite, etc. It is converted on oxidation to trichloracetic acid. With small quantities of acid it is converted into a white amorphous modification called metachloral. When boiled with potassium hydroxide it is decomposed into chloroform and potassium formate. It gives the well-known carbylamine reaction when warmed with potash and anilin.

Chloral hydrate is a hypnotic, and has long been used as a constituent of "Knock-out" drops. In medicine it is valuable on account of its hypnotic properties. It is used in acute fevers, cerebral congestions, inflammations, mania, delirium tremens, croup, insomnia, tetanus, strychnin, and cocain poisoning, chorea, and convulsions, and should be looked for in preparations intended for these disorders. Externally it is employed in alleviating foul sores, irritating ulcers, and in remedies for destroying parasites.

[1] Pharm. Zeit., 1912, 125.

It will be found usually in the form of syrups or elixirs, and often combined with bromides, Hyoscyamus, and Cannabis indica. In dandruff removers it occurs in conjuction with resorcinol. To a limited extent it is dispensed in a compressed tablet or in capsule form.

Chloral and its derivatives are included in the list of inhibited drugs, and the label of a preparation containing them is required to bear a statement of the quantity present.

When chloral is poured into water the oily mass is soon changed to colorless crystals of chloral hydrate, $CCl_3CH(OH)_2$, which is strictly speaking a chlorinated diatomic alcohol. This is the form in which chloral appears on the market. It has a peculiar characteristic odor, melts at 57–58° C., boils 97°, is readily soluble in water, alcohol, and the ordinary organic solvents including petroleum ether, in fixed and volatile, and is decomposed on distillation with sulphuric acid, chloral passing over. It does not polymerize nor does it give the rosaniline reaction of aldehydes, in fact the general aldehyde properties due to the carbonyl group are no longer apparent, which is to be expected. It liquefies when triturated with an equal quantity of menthol, camphor, thymol, or phenol. An aqueous solution of chloral hydrate reduces ammoniacal silver oxide and Fehling's solution. It slowly volatilizes. A solution of chloral dissolves morphin, quinin, and other alkaloids. The liquefied product solidifies to a crystalline mass between 35 and 50°. It does not give the iodoform reaction and is not acted upon when gently heated with nitric acid of specific gravity 1.2.

Chloral alcoholate differs essentially from chloral hydrate and is not readily soluble in water, gives the iodoform test and is acted upon by nitric acid, specific gravity 1.2.

A solution of pyrogallol in 66 per cent sulphuric acid gives a blue color when gently warmed with chloral, and ruby color with butylchloral, and a more or less violet to blue color with mixtures. On adding a large amount of water the blue color changes to yellowish and the ruby to violet.

In the general scheme of analysis chloral hydrate will appear on shaking out the acid solution with petroleum ether, and will be entirely removed in the next or ether fraction. The residue left on evaporating the solvent will be a colorless, syrupy liquid which will finally crystallize unless there is too much water present. This residue will have the characteristic odor of the substance, will give the carbylamine reaction and an aqueous solution will reduce ammoniacal silver oxide and Fehling's solution. Butylchloral hydrate is much more difficultly soluble in water than chloral hydrate and has a melting-point of 78°, does not give chloroform on treatment with alkali and reacts differently with pyrogallol.

Some little care may be necessary to distinguish between chloral and its amido compounds, and before leaving a chloral hydrate residue the

analyst can well apply a few precautionary reactions. A small amount of the residue should be warmed with potassium hydroxide, and if there is no carbylamine odor it is almost certain that no amido substances are present. If, however, the odor is obtained it may indicate acetanilid, and in order to eliminate this contingency the residue should be heated in a small Erlenmeyer on the steam-bath with dilute sulphuric acid for an hour, not allowing the concentration to become great enough to produce charring, then diluted and shaken out several times with ether. The acid solution is warmed to drive off any dissolved ether and treated with bromin water which will throw out the tribromanilin bromide if anilin sulphate is present. The bromin compound must then be separated, washed, dried, and its melting-point determined. By this means any acetanilid will be hydrolyzed, and acetic acid and anilin sulphate produced, the latter remaining in the acid solution on shaking with ether to remove the chloral. Bromal hydrate can be distinguished from chloral hydrate, since it will give bromoform on warming with dilute alkalies. Bromoform boils 148–150° in contrast to chloroform, which boils 60–62°.

Bromoform gives the carbylamine reaction, but when boiled with alcoholic potash it does not give a formate.

$$CHBr_3 + 3KOH + C_2H_5OH = 3KBr + CO + C_2H_4 + 3H_2O$$

Chloroform gives triethyl formate, which, on treatment with tartaric acid and distilled, yields formic acid.

Chloral hydrate, on boiling with magnesium oxide and water, gives chloroform and magnesium formate. Trichloracetic acid yields chloroform, but no formic acid.

Most of the methods advanced for the quantitative estimation of chloral depend upon the decomposition of the substances with alkalies and separating and measuring the chloroform produced. If the sample under investigation is a solid, the chloral hydrate should be dissolved out of the excipient with ether, the solvent evaporated rapidly but without undue heating, and the residue washed with water into a small distilling flask, which is fitted with a tube bent twice at right angles, and running into a graduate accurately calibrated. Four to five grams of slacked lime are then added to the distilling flask, which is gently heated, so that the chloroform evolved will be cooled in the tube, and collected in the graduate. After the bulk of the chloroform has come over, the heat is increased until about 10 mils of water have distilled, and then the volume of chloroform is read off. The meniscus can be broken by adding a little potassium hydroxide. The volume of the chloroform multiplied by 1.84 gives the grams of anhydrous chloral or by 2.064 the amount of chloral hydrate.

A liquid mixture may be examined in the same general way, first removing any alcohol that may be present by distillation, and then shaking

out the chloral with ether from a slightly acid solution. If a previous qualitative test has shown little else than water and chloral, the solution can be added directly to the distilling flask.

If it is desired to assay a sample of chloral hydrate, a weighed sample is placed in a graduate and treated with strong potassium hydroxide solution, keeping the mixture cool at first until the first violent reaction has ceased. The tube is then stoppered and shaken, and after two to three hours the volume of the chloroform determined.

A residue of chloral hydrate can be titrated with alkali, using litmus as an indicator. It is dissolved in water and any free acid present neutralized with barium carbonate, the filtrate treated with a known excess of N/1 sodium hydroxide and titrated back with acid. One mil N/1 alkali = .1415 gram chloral or .1655 gram chloral hydrate.

Chloral hydrate can also be determined by boiling with magnesium oxide and water under a reflux, whereby chloroform and magnesium formate result. The chloroform is then distilled, the aqueous solution acidified with tartaric acid and the formic acid distilled with steam using the details and precautions prescribed on page 627, under the determination of formic acid.

Self,[1] criticising the B. P. method of assaying chloral, recommends heating .3 gram of the sample with 1 gram aluminum powder or 2.5 grams zinc filings, 15 mils glacial acetic acid and 40 mils water for one-half hour under a reflux. The mixture is then filtered and after washing, the chlorine in the solution is determined.

The detection of small quantities of chloral, especially in the presence of chloroform, bromoform, and trichloracetic acid, can be accomplished by dissolving the residue in water faintly acid with sulphuric acid, transferring to a flask, adding a little zinc and closing the flask with cotton. When the evolution of hydrogen has ceased, the flask is warmed and the vapor escaping allowed to act on paper impregnated with sodium nitroprusside and 5 per cent piperidin. A blue coloration indicates aldehyde formed by the reduction of the chloral.

Trichlorethidene propenyl ether, $CCl_3CHO(OH)_3C_3H_5$

This ether is a condensation product of chloral and glycerin and is marketed in a glycerine solution under the name " Somnos."

Dimethylethylcarbinol chloral, $C_2H_5(CH_3)_2COCHOHCCl_3$

This product is sold under the name of " Dormiol," either in a 50 per cent aqueous solution, or in globules or capsules in an oil medium. It is soluble in alcohol, ether, and chloroform, reduces ammoniacal silver

[1] Pharm. J., 1907, 79–4.

oxide similarly to chloral, and on treatment with caustic alkali is decomposed with a precipitation of chloroform. It is gradually broken down by simply warming its aqueous solution or on exposure to the light.

Bromal, CBr_3CHO

Bromal is a heavy yellowish liquid, specific gravity 2.30 at 15°, boiling 174° C., soluble in alcohol and ether, and forming the hydrate with water.

Bromal Hydrate, $CBr_3CH(OH)_5$

This body is closely related to chloral hydrate, it forms white deliquescent crystals having a similar odor to chloral hydrate. It melts 53° C. and is soluble in water, alcohol, ether, and chloroform. It is employed for the same purposes as chloral, but will seldom be encountered in practice.

On warming with alkali it yields bromoform and a formate.

Butyl-chloral, $CH_3CHClCCl_2CHO$

Butyl-chloral is made by passing dry chlorine through acetaldehyde cooled to $-10°$ C.; on fractional distillation of the product, the fraction boiling 163–165° C. is collected. It is a colorless, oily liquid, specific gravity 1.395 at 20° C., and soluble in alcohol, ether, and water. On oxidation with nitric acid it yields trichlorbutyric acid, melting about 60° and boiling 235–238°.

Butyl-chloral Hydrate, $CH_3CHClCCl_2CH(OH)_2$

The hydrate results on adding water to butyl chloral. It occurs in crystalline micaceous scales of a pungent odor, melting 78°, readily soluble in alcohol, ether and glycerin, sparingly soluble in water and only slightly in chloroform. It does not yield chloroform when heated with alkalies or lime water. Its use is limited, but in general it is given for the same purposes as chloral.

Chloralurethane, $CCl_3CH(OH)(NH)COOC_2H_2$

This substance, also called uraline, ural, or uralium, is prepared by heating chloral with urethane (ethyl carbamate), $CO(NH_2)OC_2H_5$, and then adding sucessively hydrochloric acid and acetic acid. It forms colorless crystals, melting 103°, readily soluble in alcohol, water, and ether.

Chloral formamide, $CCl_3CHOHCONH_2$

This product, also called "chloralamide," is official in our Pharmacopœia. It occurs as lustrous, colorless, odorless crystals, readily soluble in

ordinary organic solvents, glycerin, and water, melting 114–115°. It is decomposed when heated in solution.

It is used as a hypnotic and analgesic, and should be suspected in remedies for certain forms of neuralgia and sleeplessness accompanying headache. Its melting-point is very close to that of acetanilid.

Chloralimide, $CCl_3CH=NH$

Chloralimide occurs in colorless, odorless crystals, melting 153°, readily soluble in alcohol, ether, chloroform, and oils and insoluble in water. It is employed for the same purposes as the preceding substance.

Chloralose—Anhydroglucochloral, $C_8H_{11}Cl_3O_6$

Chloralose results from the action of anhydrous chloral on glucose. It forms colorless crystals, melting 183°, soluble in alcohol and slightly in water.

It is claimed that this body will produce sleep without affecting the heart and without cumulative tendency.

Galactochloral

This body probably resembling the former in composition, occurs in lustrous leaflets, soluble in alcohol and insoluble in water.

Hypnal

Hypnal is an equimolecular mixture of chloral hydrate and antipyrin, and melts 67° C. It is readily soluble in water.

Viferral

Viferral is prepared from chloral and pyridin, and is a white powder, readily soluble in warm water, but not in water acidulated with hydrochloric acid. It melts 150–155°. It is similar to if not identical with the substance called "Polychloral," which is apparently a polymerized chloral, and readily converted by water into chloral hydrate.

Chloral Acetone Chloroform

This substance is made by heating together equimolecular quantities of chloral and trichlortertiary butyl alcohol or chloretone. The resulting product melts 65° and may be sublimed unchanged. It possesses a faint odor and taste resembling camphor, sparingly soluble in cold water, and is decomposed by acids into its components. Just how intimately the separate bodies are combined is as yet uncertain.

A solid polymeric form of chloral results when the oil is treated with anhydrous aluminum chloride. The resulting product is insoluble in alcohol, water, or acids, but dissolves in sodium carbonate solution. It gives chloroform on warming with alkali.

Trichloracetic acid, CCl_3COOH

This substance would perhaps be more properly discussed under acids, but as it is in some respects a derivative of chloral, and in some of its chemical properties bears a resemblance to that body, it will be taken up now.

It is obtained by oxidizing chloral with nitric acid, and on distillation the portion coming over at 195° is the pure acid. It boils at that temperature, melts at 52–53° C., and forms deliquescent, colorless crystals, with a pungent, suffocating odor and freely soluble in water, alcohol, and ether. Hot alkalies decompose it into chloroform and a carbonate, chloral under similar conditions yielding chloroform and a formate. It will of course give the carbylamine reaction.

Trichloracetic acid will be removed from an acid aqueous solution with ether, and may be recognized by its odor, boiling-point, and chemical properties.

There are two other chloracetic acids, monochlor, melting 62° and boiling 185–187°, and dichlor, a liquid boiling 190–191°. Neither of them will give chloroform on treatment with alkali.

All of the chloracetic acids are powerful escharotics, astringents, and hemostatics. The trichlor is the one generally used and will be found in wart and corn remedies, in liquids for local application in the nose and throat for the removal of growth, and for the removal of venereal growths, chancre, gleet, gonorrhea, etc., and for alleviating nose bleed.

Trichlorbutyric acid, $CH_3CHClCCl_2COOH$

Trichlorbutyric acid is prepared from butylchloral by oxidation with nitric acid. It forms colorless needles, slightly soluble in water, melting above 60° and boiling 235–238° C.

AROMATIC ALDEHYDES

The aromatic aldehydes may be derived from the corresponding alcohols by mild oxidation. Those with the carbonyl group attached to the nucleus differ in some particulars from those in which it is attached to the side chain, but in general their properties are similar, and those of the latter class resemble the aliphatic aldehydes very closely. Those with the aldehyde group in the nucleus do not reduce Fehling's solution,

do not form addition products with ammonia, and when shaken with alkali from a corresponding alcohol and acid.

Benzaldehyde, C_6H_5CHO

Benzaldehyde is a representative of the type with the carbonyl in the nucleus. It was formerly obtained by the decomposition of amygdalin, a glucoside occurring in bitter almonds, but is now prepared synthetically.

It is a colorless liquid, boiling 179°, specific gravity 1.05 at 15° and volatile with steam. It has a characteristic odor, is sparingly soluble in water, but readily in organic solvents. It is completely oxidized in alcoholic solution to benzoic acid, which furnishes a simple method for its determination.

Benzaldehyde is the chief constituent of oil of bitter almonds and other oils distilled from similar fruits. It is also a constituent of Cherry Laurel Water and shares its reputation with hydrocyanic acid, with which it endeavors to strike an equilibrium as benzaldehyde cyanhydrin.

Determination of Benzaldehyde, U. S. P.—Dissolve about 3 mils of freshly redistilled phenylhydrazine in 60 mils of alcohol and titrate 25 mils of this solution, which must always be freshly prepared, with half-normal hydrochloric acid V. S., using methyl orange T. S. as indicator. To about 1 gram of the Oil of Bitter almond, accurately weighed, add 25 mils of the phenylhydrazine solution just prepared and allow it to stand for thirty minutes. Add a drop of methyl orange T. S., and acidify the mixture by adding a measured excess of half-normal hydrochloric acid. Filter the mixture and wash the precipitate with small portions of distilled water until the washings cease to redden blue litmus paper. Then titrate the excess of hydrochloric acid in the filtrate with half-normal potassium hydroxide V. S. and subtract the number of mils of the half-normal hydrochloric acid V. S. used in titrating the 25 mils of phenylhydrazine solution; the difference multiplied by .053 gives the weight of benzaldehyde.

Method of Hortvet and West.—Measure 10 mils of the extract into a 100-mil flask, add 10 mils of a 10 per cent sodium hydroxide solution and 20 mils of a 3 per cent hydrogen peroxide solution, cover with a watch-glass and place on a water-oven. Oxidation begins almost immediately and should be continued from five to ten minutes after all odor of benzaldehyde has disappeared, which usually requires from twenty to thirty minutes. If nitrobenzol be present, it will be indicated at this point by its odor. When the oxidation of the aldehyde is complete, remove the flask from the water-oven, transfer the contents to a separatory funnel, rinsing off the watch-glass, add 10 mils of a 20 per cent sulphuric acid solution, and cool the contents of the funnel to room temperature under

the water tap. Extract the benzoic acid with three portions of 50, 30, and 20 mils of ether, respectively, wash the combined extracts in another separatory funnel with two portions of from 25 to 30 mils of distilled water, or until all the sulphuric acid is removed. Filter into a tared dish, wash with ether, allow to evaporate at room temperature, and finally dry overnight in a desiccator, and weigh. The per cent of benzaldehdye (B) is obtained from the weight of the acid (W) by the following formula:

$$B = \frac{0.869 \times 10 \times W}{1.045}$$

If desired the benzoic acid may be titrated, and the benzaldehyde calculated from the amount of standard alkali required for neutralization. The process is as follows: Dissolve the benzoic acid obtained as above described, except that it need not be dried in a desiccator, in 95 per cent alcohol, made neutral to phenolphthalein with N/10 sodium hydroxide, dilute with an equal volume of water, and titrate with N/10 sodium hydroxide, using phenolphthalein as indicator. The per cent of benzaldehyde (B) is calculated from the mils of N/10 alkali (V) by the following formula:

$$B = \frac{V \times 0.01061 \times 10}{1.045}$$

Cinnamic Aldehyde, $C_6H_5CH : CHCHO$

This aldehyde is the chief constituent of oils of cinnamon and cassia. It is a yellowish oil with a characteristic odor, boiling about 245° C. under ordinary pressure with partial decomposition or at 128–130° at 20 mm. pressure, readily soluble in all the organic solvents, from which it may be extracted by shaking with sodium bisulphite solution. It oxidizes gradually and samples which have stood for any length of time will contain free cinnamic acid. Oxidation with peroxide converts it to cinnamic acid with the simultaneous formation of a little benzoic.

Estimation, U. S. P. Method.—Introduce 10 mils of the oil into a 200-mil flask with a long graduated neck (cassia flask) by means of a pipette, add 50 mils of a saturated solution of sodium sulphite, which has been carefully rendered neutral to phenolphthalein by means of acetic acid, heat the mixture in a bath containing boiling water and shake the flask repeatedly, neutralizing the mixture from time to time by the addition of a few drops of dilute acetic acid. When no coloration appears, upon the addition of a few more drops of phenolphthalein and heating for fifteen minutes, cool, and when the liquids have separated completely, add sufficient of the sodium sulphite solution to raise the lower limit of the oily layer within the graduated portion of the neck and note the volume

of the residual liquid. It shows not less than 80 per cent by volume, of cinnamic aldehyde.

It is found that cinnamic aldehyde, both pure, and as it occurs in cinnamon and cassia oils, may be quantitatively precipitated in the form of semioxamazone:

$$C_6H_5 \cdot CH : CH \cdot CH : N \cdot NH \cdot CO \cdot CO \cdot NH_2,$$

by treating an aqueous suspension with a solution of semioxamazide in hot water.

About .10 gram of the aldehyde is emulsified by agitation with 100 mils of water and treated with .25 to .35 gram of semioxamazide dissolved in 15 mils of hot water; the mixture is well shaken together, occasionally, for three hours, then allowed to stand for twenty-four hours. The crystalline cinnamic-aldehyde semioxamazone is then collected on a tared Gooch filter, washed with cold water, dried at 105° C. for about four or five hours, then weighed. The weight of semioxamazone multiplied by the factor .6083 gives the amount of cinnamic aldehyde present. For the determination of the amount of aldehyde in cinnamon and cassia oils, from .15 to .2 gram is employed.

To determine the amount of cinnamic aldehyde in cinnamon or cassia barks, from 5 to 8 grams of the finely ground material are distilled with steam, until about 400 mils of distillate have been collected. The volatile oil is extracted from the distillate by shaking out three or four times with ether, and after distilling off the ether, the oil is emulsified and treated with semioxamazide as described above.

Salicylic Aldehyde, $C_6H_4(OH)CHO$

O-hydroxybenzaldehyde, sometimes called "salicylous acid" may be obtained by oxidizing salicin with chromic acid. It possesses the properties of a phenol and an aldehyde. It is a colorless oil with a penetrating odor, boiling 196°, specific gravity 1.165–1.172 at 15° C., somewhat soluble in water to which solution ferric chloride imparts a violet color, and dissolving in all the ordinary organic solvents.

Salicylic aldehyde occurs naturally in flowers of Spiræa ulmaria.

The *p*- and *m*-aldehydes are solids, melting 116° and 104° respectively.

Salicylic aldehyde on treatment with sodium acetate and acetic anhydride is converted to coumarin, the odorous principle of tonka bean.

Anisic aldehyde, $C_6H_4(OCH_3)CHO$

Anisic or *p*-methoxybenzaldehyde is obtained on oxidizing anethole, $C_6H_4(OCH_3)CH : CH : CH_3$, from oil of anise. It is a colorless oil with a penetrating odor boiling 248°.

Cuminic Aldehyde, $C_6H_4(CH_3)_2CHCHO$

Cuminic or paraisopropyl benzoic aldehyde, incorrectly called cuminol, is the constituent of oil of cumin, to which it owes its odor and more prominent properties, and also occurs in oil of Roman chamomile.

It is a yellowish oil with a persistent odor, and acrid burning taste, specific gravity .972 at 13°, boiling 232° or at 109.5° under 13.5 mm., soluble in alcohol and ether.

Vanillin, $C_6H_3OH \cdot OCH_3 \cdot CHO$ 4 : 3 : 1

Methyl protocatechuic aldehyde or vanillin is one of the valuable constituents of vanilla beans, and also occurs in Siam benzoin and asafetida. It is not prepared in a commercial way from either of these sources, but from eugenol, an aromatic unsaturated phenol occurring in oil of cloves.

It occurs in colorless prisms having an aromatic odor and a vanilla-like taste, melting 80–81°, boiling 285°, subliming when cautiously heated, slightly soluble in water and readily in the organic solvents. Its aqueous solution gives a blue color with ferric chloride.

Vanillin possesses the characteristics of both a phenol and an aldehyde, and is therefore removed from its solution in organic solvents by both alkalies and sodium bisulphite.

It is used to a limited extent in medicine as a tonic, stimulant, and aphrodisiac, and its presence is recognized without difficulty by its characteristic odor.

Coumarin of course has an odor which simulates that of vanillin, but may be distinguished from the latter as it is not removed from its solution in ether by sodium hydroxide.

Vanillin reduces ammoniacal silver oxide. When heated with dilute hydrochloric acid under pressure to 200° it yields protocatechuic aldehyde and methyl chloride. When fused with potash, protocatechuic acid results.

On exposure in a moist or finely divided state it is oxidized to vanillic or methylprotocatechuic acid, melting 207°, which gives no color with ferric chloride. It yields vanillyl alcohol melting 115° on reduction.

Vanillin gives a characteristic color when heated with hydrochloric acid and phloroglucinol. It gives a deep-bluish violet color when rubbed with resorcinol and hydrochloric acid.

Vanillin as now found on the market is usually quite pure, but it was formerly contaminated with acetyl isoeugenol, due to incomplete purification, and it also was sophisticated by admixture with benzoic acid and acetanilid

Folin's Method for Determining Vanillin.—*Solutions Required:* (1) An aqueous solution of pure vanillin to be used as a standard. This should be made of such a strength that 10 mils contains 1 mg. of vanillin.

(2) The phosphotungstic-phosphomolybdic acid reagent, prepared as follows: To 100 grams pure sodium tungstate and 20 grams phosphomolybdic acid (free from nitrates and ammonium salts) add 100 grams syrupy phosphoric acid (containing 85 per cent H_3PO_4) and 700 mils water; boil over a free flame for $1\frac{1}{2}$ to 2 hours; then cool, filter if necessary, and make up with water to a volume of 1 liter. An equivalent amount of pure molybdic acid may be substituted for the phosphomolybdic acid.

(3) A solution of pure sodium carbonate saturated at room temperature.

(4) A solution containing 5 per cent basic and 5 per cent neutral lead acetate.

Vanillin (and also other mono-, di-, and trihydric phenol compounds) when treated in acid solution with the phosphotungstic-phosphomolybdic reagent above described gives on the addition of an excess of sodium carbonate a beautiful deep-blue color admirably suited for quantitative colorimetric work.

Five mils of the vanilla extract to be examined are transferred by means of a pipette to a 100-mil volumetric flask and about 75 mils cold tap water are added: 4 mils of the lead acetate solution are then poured in and the mixture made up to volume with water.

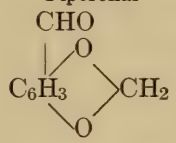
The contents of the flask are then rapidly filtered through a folded filter paper; and 5 mils of the filtrate are transferred by means of a pipette to a 50-mil volumetric flask. In another 50-mil volumetric flask is placed 5 mils of the standard vanillin solution; then 5 mils of the phosphotungstic-phosphomolybdic reagent is added to each flask, the reagent being allowed to run down the neck of the flasks in order that any vanillin adhering thereto may be washed down. After shaking, the flasks are allowed to stand for five minutes and are then filled to the mark with saturated sodium carbonate solution. After inverting the flasks two or three times in order that the contents may become thoroughly mixed, they are allowed to stand for ten minutes, by which time the precipitation of sodium phosphate is complete. The contents of the flasks are then rapidly filtered through a folded filter paper and the color of the resulting clear deep-blue solutions compared by means of a Dubosc colorimeter. The standard solution is best placed at 20 mm. as experiment has shown that the color produced by the amount of vanillin contained therein (1 mg. in 100 mils) is most accurately and easily read at this point.

In this, as in all other colorimetric methods, a slight cloudiness of the solution to be read, by cutting off more light than the standard, gives

a reading much too low, with correspondingly high results; consequently no solution should be read which is not absolutely clear after filtration.

The calculation of the results is not complicated. When 5 mils of the solution (previously diluted 5 : 100) is taken, this corresponds to .25 mil of the original solution. If 10 mils are taken they correspond to .5 mil of the original. Since .5 mg. vanillin is used as a standard and with the standard set at 20 (mm.) $.5 \times 20/R = X$ where R is the colorimeter reading of the unknown and X is the amount of vanillin in mgs. present in the volume of the original extract used in the final color comparison; 100 X divided by the volume of the extract taken expressed in mgs. gives the result in grams per 100 mils.

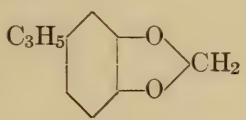
Piperonal



This substance, which is chemically the methylene ester of protocatechuic aldehyde, is also known as heliotropin. It may be obtained by the gradual addition of potassium permanganate to a solution of potassium piperate, obtained by the fusion of piperin, and forms white, shiny crystals with a pleasant characteristic odor of heliotropin, melting 37°, slightly soluble in water, readily in alcohol and ether. It does not keep well except in alcoholic solution.

It is used medicinally as an antiseptic and antipyretic, and will be found in remedies for skin diseases and fevers.

Piperonal is now made from safrole,



by saponifying and then oxidizing with permanganate and sulphuric acid.

When heated to 200° under pressure with dilute hydrochloric acid it gives protocatechuic aldehyde and carbon.

Piperonal may be adulterated with vanillin and products formed during its manufacture.

KETONES

As medicinal agents the ketones of the aliphatic series have little importance, acetone is employed as a solvent and vehicle to some extent and methylisopropyl ketone has hypnotic properties. Of the aromatic ketones acetophenone and benzophenone with some of their derivatives,

have attained considerable importance, and the cyclic ketone camphor is a valuable medicinal agent.

In the aliphatic series the ketones form an homologous series isomeric with the aldehydes, and are closely related to them in all reactions affecting the carbonyl group, which is common to both classes. Ketones form crystalline compounds with bisulphite, and oximes with hydroxylamine, and also react with phenylhydrazine and hydrocyanic acid. They are produced by the oxidization of secondary alcohols. They differ markedly from the aldehydes on oxidation, for, while the aldehydes are oxidized with ease to an acid containing the same number of carbon atoms, the ketones are only acted upon by stronger oxidizing agents, and are broken up, yielding products containing a smaller number of carbon atoms. Ketones do not reduce ammoniacal silver, nor restore the color to fuchsin bisulphite, neither do they polymerize though they form condensation products under certain conditions. Futhermore they do not form addition products with ammonia nor combine with alcohols to form acetals.

The lower members of the ketone series are colorless, mobile, odorous, volatile liquids soluble in water, alcohol, and ether. As the number of carbon atoms increases, the boiling-point rises and the solubility in water decreases. The higher members are heavy solids. Ketones give the corresponding secondary alcohols on reduction. A secondary alcohol is not the sole product of reduction, but is usually accompanied by varying quantities of pinacones, acetone for example yielding acetone pinacone, $(CH_3)_2C(OH)\cdot C(OH)(CH_3)_2$. Pinacones on distillation with dilute sulphuric acid, yield pinacolines, that from acetone pinacone is a colorless liquid boiling 100° and having a menthol-like odor.

Ketones are acted on by phosphorus pentachloride with formation of dihalogen derivatives of paraffins. When treated with dehydrating agents they undergo a form of condensation with elimination of water, two or more molecules taking place in the reaction, thus acetone gives mesityl oxide, $C_6H_{10}O$, and phoron, $C_9H_{14}O$.

Acetone, CH_3COCH_3

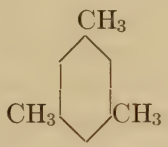
Acetone has a limited use in medicine as a mild alterative and anthelmintic, and locally in certain forms of irritation where it is administered as a liniment. It is also used as a vehicle and does not have to be declared on the label.

In liniments intended for local application it will be found combined with extracts and oils of arnica, calendula, turpentine, cade, and similar products, thujone, camphor, etc. Some of these mixtures are recommended as bactericides and for the absorption of calluses, tumors, goiter and like growths.

Acetone is a colorless, mobile liquid, specific gravity .792 at 20° C., boiling 56–57° with a peculiar, characteristic ethereal odor, and miscible in all proportions with water, alcohol, ether, chloroform, and volatile oils. When shaken with concentrated sodium bisulphite, it forms a crystalline compound which is readily soluble in water but insoluble in alcohol, and decomposed by dilute acids or alkalies. It forms acetoxime with hydroxylamine, a crystalline substance melting 59° C. With phosphorus pentachloride it yields beta-dichlorpropane, $(CH_3)_2CCl_2$.

Acetone gives the iodoform reaction in the cold. It does not reduce ammoniacal silver, nor give the rosaniline test.

When saturated with dry hydrogen chloride it yields mesityl oxide and phoron, and when distilled with concentrated sulphuric acid it yields mesitylene, a derivative of benzol. Mesityl oxide is a colorless oil, boiling 130° C. with a menthol odor. Phoron is a colorless, crystalline solid melting 28°, and boiling 196°, with a pleasant aromatic odor. Both substances are reverted to acetone on boiling with dilute sulphuric acid. Mesitylene



is symmetrical trimethylbenzene, a colorless, mobile, fragrant liquid boiling 163°.

When molecular proportions of acetone and chloroform or acetone and bromoform are treated with caustic alkalies, chloretone melting 80–81° and brometone melting 167° are found respectively. Both of these substances are trichlor and tribrom derivatives of tertiary butyl alcohol.

On chlorinating acetone, monochloracetone, CH_3COCH_2Cl, is one of the products. It is a colorless, pungent liquid, specific gravity 1.162 at 16°, boiling 105–106°, miscible with alcohol, ether, and chloroform and insoluble in water.

For the detection of acetone, the distillate from a mixture should be employed, and if the distillate contains any essential oils they should be removed by shaking out with salt and petroleum ether, and the salt solution again distilled. If acetone is present, the distillate will give a precipitate of iodoform in the cold on adding a little sodium hydroxide and iodin solution. It will also give characteristic tests with salicylaldehyde and sodium nitroprusside. The former is carried out as follows: 10 mils of the liquid are treated with 1 gram of solid potassium hydroxide, and 10 drops salicylaldehyde and warmed to 70° C. In presence of acetone a purple-red contact ring develops. If the hydroxide is all dissolved

before the reagent is added, the liquid becomes yellow, reddish and purple-red

The Nitroprusside Reaction.—Shake five drops of the ketone with 2 mils of cold water. If the substance does not dissolve completely, filter through a wet filter. Add to the clear solution two drops of a 1 per cent aqueous solution of sodium nitroprusside, and then two drops of sodium hydroxide solution (1 : 10). Without any unnecessary delay, carefully note the color, and then quickly divide the solution into two equal portions, *a* and *b*, in small glass " weighing-tubes." To portion *b* add three drops of glacial acetic acid, and immediately note the color. Allow both solutions to stand for twenty minutes, and again carefully compare the color of each with the color standard.

Many of the aldehydes as well as ketones give colorations in this test; but its most important practical application is its use as a convenient specific reaction for acetone and acetophenone. It distinguishes these ketones readily from all related ketones with which either is likely to be confused.

In the case of acetone, portion *a* at first is orange, but changes to a clear yellow within twenty minutes. Portion *b* after the acidification with acetic acid is a red when viewed against a white background, with a very slight tendency to purple, that is most noticeable when the solution is viewed by a strong transmitted light. This hue will be found unchanged at the end of twenty minutes, though its intensity will have fallen about one tint. The persistency of this hue in acetic-acid solution is the most characteristic part of the test when used to distinguish acetone from its homologues.

In the case of acetophenone, the color of portion *a* is at first red with a very slight tendency to violet-red, just as in part *b* of the acetone test after acidification. This changes to yellow before the end of twenty minutes. Portion *b* upon acidification with acetic acid changes at once to a strong blue, whose hue is not materially changed at the end of twenty minutes, although it will have faded nearly one tint.

The most characteristic part of the acetophenone test is the strong blue coloration of portion *b*. Homologues of acetophenone, $CH_3 \cdot CO \cdot R$, like methyltolyl- and methylxylyl ketone, give pale violet or bluish colorations. Fatty aromatic ketones, like ethyl-phenyl ketone, which contain no methyl radical in combination with $CO \cdot R$, appear not to give any blue coloration at all.

Sodium-nitroprusside solution does not keep very well, and should not be more than a few days old when used.

Method for the Determination of Methyl Alcohol and Acetone in Drug Products.—A measured portion of the sample is diluted and filtered if deemed advisable and the whole or a convenient aliquot distilled into

such a volume that the distillate shall contain not more than 30 per cent volatile matter other than water.

If volatile oils are present, the sample, either before or after distillation, is freed from them by one of the following methods:

(*a*) Shake with magnesium carbonate and filter, taking precautions to avoid loss by evaporation.

(*b*) Saturate with salt and shake with petroleum ether. Separate the aqueous layer and if necessary repeat once or twice with fresh petroleum ether. Wash the successive or combined petroleum ether portions with saturated salt solution and add the wash water to the main liquid and distill.

Acetone.—An appropriate aliquot of the distillate is added to a convenient volume of a solution containing approximately 140 grams potassium iodide and 114 grams sodium hydroxide per liter. An excess of a standardized solution of sodium hypochlorite is introduced, and the container stoppered and shaken for at least one minute. The solution is then acidified with dilute hydrochloric acid, care being taken not to allow the mixture to become hot. An excess of a standardized solution of sodium thiosulphate is introduced and the excess determined by means of the sodium hypochlorite solution, starch solution being used as indicator. Six atoms of iodin convert one molecule of acetone into iodoform.

Methyl Alcohol.—An appropriate aliquot of the distillate is freed from acetone by conversion into iodoform with iodin and alkali. The iodoform filtered off or shaken out with petroleum ether or chloroform, the solvent being washed with saturated salt solution and the washings added to the main liquid. If preferred, a combination filtration and shake-out method may be used to eliminate the iodoform. The liquid is then distilled, the distillate diluted to a definite volume and the methyl alcohol estimated from the refractive index as given on page 535. For approximate results the density tables for ethyl alcohol may be used.

Determination of Acetone by the Mercuric Iodide Method. Denigès.[1]—The reagent is prepared by dissolving 5 grams of mercuric oxide in 100 mils of water to which 20 mils of sulphuric acid have been added. Acetone in aqueous solution may be detected by adding 2 mils of this reagent to 2 mils of the solution in a test-tube and plunging the tube into boiling water. If no acetone is present, no precipitate will form within ten minutes. If the acetone is in alcoholic solution, water must be added prior to the addition of the reagent. Acetone may be estimated by taking 25 mils of the solution containing it—first diluting with water if the solution is an alcoholic one—adding 25 mils of the reagent, and corking tightly in a strong flask of 90 mils capacity. The flask is set in a water-bath, which is raised to the boiling-point, and kept boiling for ten minutes.

[1] J. Soc. Chem. Ind., 1899, page 179.

The flask is then removed from the bath, allowed to cool, and the precipitate is collected on a weighed filter, washed with cold water, and dried. The weight of the precipitate multiplied by .06 (theoretically .0584) gives the weight of the acetone in the 25 mils of solution taken.

Methyl alcohol and acetone can be detected in tincture of iodin by destroying the iodin with thiosulphate and distilling off a few mils through a long vertical condenser bent at about 50 cm. from the flask. Part of the distillate is treated according to the methods for detecting methyl alcohol and another portion tested for acetone.

Determination of Acetone in Presence of Ethyl Alcohol.—A portion of the sample, containing about .05 gram of acetone, is placed in a 750-mil flask, 300 mils of freshly prepared lime-water is added, the flask is closed loosely with a rubber stopper, and its contents heated to 35° C.; 5 mils of N/5 iodine solution is then added, drop by drop, and after shaking for five minutes, a second 5 mils is added, and so on until 40 mils in all has been introduced. After ten minutes, starch solution is added, the mixture cooled, acidified with 15 mils of N/1 sulphuric acid, and the excess of iodin titrated with N/10 thiosulphate solution. The number of mils of N/5 iodin solution used is multiplied by .00193 to obtain the quantity of acetone in the portion of the sample taken. If, during the addition of the iodin, the color persists after thorough agitation, more lime-water should be added. About .8 mil of N/5 iodin is absorbed by 1 mil of ethyl alcohol. When the sample contains only about 1 part of acetone and 100 parts of ethyl alcohol, the results are not very trustworthy, but in samples containing 1 part of acetone and 10 parts of ethyl alcohol the results are accurate and concordant.

Acetone-resorcinol

When a mixture of acetone and resorcinol is treated with hydrochloric acid gas, small prisms melting 212–213° having the composition $C_{15}H_{16}O_4 + H_2O$ are produced. The product is insoluble in water, alcohol, ether, and chloroform, but dissolves in alkaline solutions. It is used as an antiseptic.

Benzylideneacetone, $C_6H_5CH=CHCOCH_3$

This product, known as methyl cinnamyl ketone, methyl styrylketone, or acetocinnamone, forms colorless crystals melting 42° with a cumarin odor. It is soluble in the ordinary organic solvents.

Salacetol, $C_6H_4(OH)CO_2CH_2COCH_3$

It forms fine white to faintly reddish needles, melting 71° C., soluble in alcohol, ether, chloroform, fixed oils, and slightly in water. It is used as an antiseptic and antirheumatic.

Sodium Lygosinate, $CO=(CH:CHC_6H_4ONa)_2 7H_2O$

This substance is the sodium salt of dioxy-dibenzal acetone. It occurs in glossy, greenish prisms, soluble in cold alcohol, easily soluble in hot alcohol and in glycerin. Its aqueous solution has a ruby-red color and is alkaline in reaction.

On ignition, 1 gram of sodium lygosinate leaves a residue of sodium carbonate weighing .243 gram. From the aqueous solution acids precipitate a thick yellow precipitate of diortho-cumarketone. The solution is fairly stable when kept in a cool place, protected from the air, and is not decomposed on boiling, but is decomposed by weak acids, even the carbonic acid of the air. Its powder produces sneezing. It is used as an antiseptic and bactericide in gonorrhœa and similar ailments.

Methyl heptenone, $CH_3 \cdot C(CH_3)=CHCH_2CH_2COCH_3$

Methyl heptenone is an unsaturated ketone found in certain oils such as linalœ, citronella, and lemon-grass. It is a colorless, mobile, inactive liquid with an amyl acetate-like odor. It boils 170–174°, readily forms a bisulphite compound and a semicarbazone melting 136–138°.

AROMATIC KETONES

The only aromatic ketones of importance in medicine are acetophenone camphor and thujone, though carvone and fenchone will sometimes occur as the flavoring principles in some elixirs and cough remedies.

The ketones have the general formula R—CO—R′, where R and R′ represent different or identical radicles, one of which must of course be aromatic.

Acetophenone, $C_6H_5COCH_3$

Acetophenone or phenyl methyl ketone is known in medicine under the name of Hypnone, and is employed as an hypnotic for insomnia.

It occurs in laminary crystals, melting 14° C., so that it will often be encountered as a liquid, and boiling at 202°. It has a pungent taste and an odor recalling that of orange blossoms. It is soluble in alcohol, ether, chloroform, fatty oils, and to a slight extent in water.

On reduction it yields phenyl methyl carbinol, $C_6H_4CH(OH)CH_3$, and on oxidation it is resolved into benzoic acid and carbon dioxide. It reacts with hydroxylamine to form an oxime, and with phenyl hydrazine to give an hydrazone.

Its low melting-point, odor and ketone-like properties are sufficient for its identification.

Benzophenone, $C_6H_5COC_6H_5$

This body forms crystals melting 48–49°.

Trioxybenzophenone, $C_6H_4OHCOC_6H_3(OH)_3$

Trioxybenzophenone or salicylresorcinol ketone, is obtained by the interaction of salicylic acid and resorcinol. It melts 133° C. and is slightly soluble in water, but dissolves in hot alcohol and benzol. It is used as n antiseptic, antipyretic, and analgesic.

Oxyphenylbenzylketone $C_6H_5CH(OH)COC_6H_5$

This ketone, which is known as Benzoiin and bitter almond oil camphor, is a reaction product of benzaldehyde, potassium cyanide, and ethyl alcohol. It forms colorless crystals, melting 135–137°, soluble in alcohol and hot water.

It has antiseptic properties and is sometimes used in ointments for ulcers and varicose veins.

Lowry in the new edition of Allen divides the cyclic ketones into four groups.

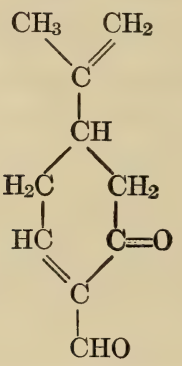
a. $C_{10}H_{18}O$ group, with a single ring: type menthone.

b. $C_{10}H_{16}O$ group, with a ring and a double bond or two double bonds: type camphor.

c. $C_{10}H_{14}O$ group, with a ring and two double bonds, two rings and one double bond, or three rings.

d. Ketones with more or less than 10 carbon atoms such as maticocamphor.

Carvone, $C_{10}H_{14}O$



This ketone occurs in the *d*-form in caraway and dill oils and in the *l*-form in spearmint oil. None of these oils are of special interest to the

drug chemist. At the present time by far the greater amount of spearmint oil is used in this country as a flavoring agent for chewing gum.

Carvone is a colorless liquid with a strong odor suggestive of caraway. The *d*-form boils 224° C., specific gravity .9598 at 20° $(\alpha)_D = +62.07°$, the *l*-form has practically the same constants with a minus rotation.

It does not add bisulphite, but yields a well crystallized oxime, melting 72°, inactive form 93°. Its phenylhydrazone melts 109–110° and its semicarbazide 54–56°. It also forms a crystalline compound with hydrogen sulphide when an ammoniacal alcoholic solution is treated with this gas.

For the determination of carvone in oil of spearmint the following methods appear to give satisfactory results:

Walther Method.—Two to 5 grams of carvone or the carvone-bearing oil are placed in a wide-neck flask and 10 grams of a freshly prepared aqueous solution (2 : 3), of hydroxylamine hydrochloride added.

Then add 25 mils aldehyde free absolute alcohol and 2 grams bicarbonate sodium, connect the flask with a return-flow condenser, and heat to gentle boiling on a water-bath.

After cooling to 25°, add 6 mils HCl (1.12), and transfer to a 500-mil volumetric flask, rinsing out the condenser and flask with dilute HCl, followed with water. Filter, and in 25–50 mils of the filtrate titrate the excess of hydroxylamine.

The titration of the hydroxylamine is carried out as follows:

Methyl orange is added (about 1 drop), and the mineral acid neutralized with alkali. Then phenolphthalein is added and the hydroxylamine titrated with N/10 NaOH.

The difference between the titration corresponding to the weight of hydroxylamine taken and that corresponding to the hydroxylamine left represents the amount converted into carvoxime.

Each mil of N/10 NaOH is equivalent to .015 gram carvone.

Nelson [1] finds this method satisfactory for determining pulegone, thujone, menthone, and camphor, but not fenchone.

H. Labbe Method.—This method rests on the fact that carvone is dissolved easily in a boiling solution of sodium bisulphite with the formation of a dihydro-di-sulphonate, of which the constitution has been established.

First Method of Determination.—Five grams of the oil are placed in a little flask, fitted with a ground-in condenser, and about 15 grams of sodium bisulphite dissolved in water with Na_2CO_3 are added. To render the boiling regular, a few pieces of porcelain are put in the flask. After $1\frac{1}{2}$ hours boiling, allow to cool thoroughly, and take up the residual oil with ether, washing out condenser and flask with the same solvent, and separate the aqueous layer in a small separatory funnel.

[1] J. Ind. Eng Chem., 1911, 3, 588.

The ether solution is dried carefully with anhydrous sodium sulphate, filtered into a small weighed flask, the major portion of the ether evaporated in a partial vacuum, and the last traces by gentle heating. The increase in weight gives the hydrocarbons, or constituents not carvone.

Second Method of Determination.—Since carvone on simply heating with a solution of sodium bi-sulphite and sodium carbonate furnishes a dihydro-di-sulphonate derivative which is very soluble, one is able, by using a titrated solution of bisulphite, to calculate from the dimunition in strength in SO_3 after boiling, the proportion of carvone.

To titrate the solution of bisulphite before and after, a centinormal solution of iodin in potassium iodide is used, which, as has been demonstrated has no action on the dissolved carvone derivative.

One gram to $1\frac{1}{2}$ grams of carvone and 10 mils of a saturated $NaHSO_3$ solution containing .2–.3 gram $NaHSO_3$ per mil are used for the estimation.

The heating is effected as in the first method except that the upper end of the condenser is fitted with a U-tube trap filled with a freshly alkaline solution to restrain any liberated SO_2.

After cooling, the SO_2 is titrated in a suitably diluted aliquot.

By this method, an absolutely pure carvone showed 100.3 per cent and a 97 per cent commercial carvone 96.9 per cent.

The titration of the $NaHSO_3$ is expressed in SO_2, and the SO_2 consumed by the carvone, shown by the difference in titration, goes to form $C_{10}H_{14}O(SO_3NaH)_2$. Therefore two molecules of SO_2 consumed correspond to one molecule of carvone present.

Camphor, $C_{10}H_{16}O$

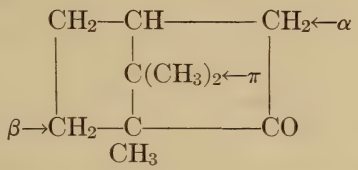
The dextro camphor, Formosa or Japan camphor, is the official or gum camphor and occurs in the camphor laurel, Cinnamonum camphora (Lauraceæ), a large tree growing in southern China, Japan, and several adjacent islands. The camphor is found dissolved in a volatile oil, found most abundantly in the roots, but is generally distributed throughout the entire tree. *d*-Camphor also occurs in small quantities in a number of essential oils such as sassafras leaves, cinnamon root, spike, rosemary, sage, etc. The *l*-form occurs in the oils of feverfew and tansy.

Artificial camphor is now prepared to a considerable extent and is a commercial article. When properly prepared and purified it can be distinguished from the natural only by having no optical rotation. By mixing equal parts of *d*- and *l*-camphors obtained from natural sources, a racemic camphor is obtained which is identical in every respect with the synthetic.

In making camphor artificially one of the products obtained is pinene hydrochloride. This substance forms a white crystalline mass which

closely resembles camphor, and has been sold as artificial camphor or turpentine camphor. It is soluble in alcohol but not in water, melts 125° and boils about 208°. It is used as an antiseptic both externally and internally, and among its other uses is recommended for checking the flow of perspiration. The presence of the halogen is readily detected by heating it on a copper wire and noting the green color produced.

The structural formula of camphor is as follows, and it forms three classes of derivatives, α, β and π, the particular portion of the nucleus effected being indicated.



Camphor is considered valuable for a number of different disorders and plays an extensive rôle in medicine. It is a stimulant and sedative according to the dose, also antispasmodic, anaphrodisiac, expectorant, carminative, and diaphoretic. Possessing as it does all these properties, it is combined with a number of other drugs which are dispensed in the form of pills and tablets.

The best known preparations containing camphor are of course the official spirit containing 10 per cent of the substance in alcohol, camphor liniment or camphorated oil containing 20 per cent of camphor in olive or cottonseed oils; soap liniment or liquid opodeldoc containing 4–5 per cent camphor; camphorated tincture of opium or paregoric, camphor cerate, and camphor water.

Camphor is an ingredient of Warburg Tincture and of inhalants both of oil and glycerin.

The common combinations used in pills or tablets include coryza formulas where the camphor functionates with quinin, morphin, atropin, and ammonium chloride, sometimes with aconite; Sun cholera mixture, consisting of camphor, opium, rhubarb, Capsicum, and peppermint; rhinitis mixture of camphor, quinin, and belladonna; and brown mixture of camphor, licorice, opium, benzoic acid, ammonium chloride, tartar emetic, and anise. Other mixtures include those of camphor with opium and Hyoscyamus; with opium and tannic acid; with valerian and Hyoscyamus; with morphin, ipecac, and potassium nitrate; with Podophyllum and ipecac; with salol, opium, bismuth subnitrate, and peppermint, etc.

Camphor is often dispensed in ointments intended to allay congestion, rheumatism, and sprains. It will be found with menthol and boric acid; quinin, turpentine, phenol, and opium; with mustard oil and aromatic balsams, etc.

As ordinarily encountered camphor occurs in blocks or masses which are white and translucent, or in small crystals called " flowers of camphor." The odor is characteristic and the taste pungent and aromatic. Camphor melts at 175° C., boils 204° C., and is inflammable, burning with a luminous smoky flame. $(\alpha)_D = \pm 44.22°$ in 20 per cent alcoholic solution. It is very sparingly soluble in water, but goes into solution in all the organic solvents, and in fixed and volatile oils. When triturated with menthol, thymol, phenol, or chloral hydrate liquefaction takes place. When thrown on the surface of clean water it goes through a rapid whirling motion which is arrested by the addition of a very small quantity of oil.

On exposure to the air it is slowly volatile, and when moderately heated sublimes without leaving a residue.

Camphor does not combine with bisulphites, but it does form a well-defined oxime melting 118–119°, and a semicarbazone melting 236–238°. To prepare camphor oxime a gram or its proportional amount of the substance is dissolved in 15 mils alcohol, treated with an equivalent amount of an aqueous solution of hydroxylamine hydrochloride 1–1 and 1.5 grams sodium hydroxide, and warmed under a reflux for an hour or two. It is well to allow the mixture to stand for about twelve hours after this treatment, and on adding considerable water and enough acetic acid to neutralize the alkali, the oxime will be precipitated. It can be crystallized out of hot dilute alcohol.

The semicarbazone of camphor may be prepared by dissolving one gram of semicarbazide hydrochloride and 1.23 grams sodium acetate anhydrous in the smallest amount of water possible, and adding the mixture to one gram of camphor in absolute alcohol. After warming the solution, it is stoppered and allowed to stand overnight, and the semicarbazone is then precipitated by water and recrystallized from alcohol.

Upon reduction camphor is converted into borneol, and on oxidation to camphoric acid and further to tribasic camphoronic acid.

Camphor will absorb gaseous hydrogen chloride, nitrogen peroxide, and sulphur dioxide, forming liquids from which the gases are liberated on the addition of water. The sulphur dioxide compound is used as a disinfectant.

The odor of camphor is generally a sufficient indication of its presence in a medicinal preparation. There will seldom if ever be any instances where other things will mask the camphor odor, though camphor may often mask the odor of other ingredients, especially menthol.

The only substances which might be confused with camphor from the point of view of odor are pinene hydrochloride, monobromated camphor, and chloretone.

If it is necessary to go further with the identity, the camphor can be conveniently converted to the oxime and its melting-point determined.

The oxime has a peculiar odor suggestive of camphor, but more intense and less pleasing.

Much work has been done on the estimation of camphor and very little of it is of any value to the drug analyst.

The extensive use of camphor in medicine and the fact that the Pharmacopœia includes preparations which must contain definite quantities of camphor make it imperative that there should be a reliable method of assay. There have been in vogue for some time procedures depending on the rotation of an alcoholic, benzol, or oil solution and on the loss by evaporation, but they are open to objection, and in certain instances the results might easily be misinterpreted. Artificial camphor is without rotatory power, natural camphor might contain a portion of the lævo body, the rotation varies with the strength of the solvent, and fixed oils themselves on heating often undergo loss or gain in weight. These are a few of the reasons which call for a method based on a more substantial foundation.

Camphor, being of ketonic character, forms with hydroxylamine a well defined oxime, $C_{10}H_{16}NOH$, and advantage has been taken of this property in assaying camphor preparations, the procedure being based on Walther's [1] carvone estimation. The procedure is simple and may be applied directly to spirit of camphor. Of the sample 25 mils are measured into an Erlenmeyer flask of 100 mils capacity, 2 grams of sodium bicarbonate are added, and then, accurately, from a burette, 35 mils of a hydroxylamin solution (20 grams $NH_2OH \cdot HCl$+30 mils H_2O+135 mils absolute alcohol aldehyde free). The flask is connected with a reflux condenser, and heated to gentle boiling for two hours; it is then cooled to 25° C., treated with a mixture of 6 mils hydrochloric acid (1.12 specific gravity+6 mils water) transferred to a 500-mil volumetric flask, rinsing out the condenser and flask with water, and finally made up to volume; 50-mil portions are filtered off and titrated as follows: Methyl orange is added and the mineral acid neutralized with normal alkali, then phenolphthalein is added and the hydroxylamine hydrochloride titrated with N/10 alkali. A blank must be run, using the same amount of hydroxylamine solution and 25 mils of alcohol to correspond with the spirits of camphor, the difference in titrations representing the hydroxylamine converted into camphor oxime. Each mil of tenth-normal sodium hydroxide is equivalent to .01509 gram of camphor.

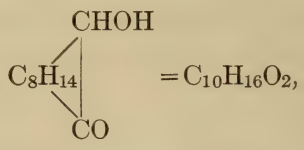
The writer has sometimes obtained good results with this method and again has obtained figures which were difficult to explain. The same report comes from other workers. It may be stated, however, that with a pure camphor carefully freed from water and all impurities it is possible to get results which render the method available in analytical work. It

[1] Pharm. Centralhalle, 1900, 41 : 613.

is probable that in case where peculiar results were obtained the fault was due to the grade of camphor employed, or to the personal equation of the worker.

Oxaphor

Oxaphor is a 50 per cent solution of oxycamphor.



a derivative of camphor in which a hydrogen atom has been replaced by a hydroxyl group.

It is a white crystalline powder, neutral in reaction, melting at 203 to 205° C. It is soluble in about 50 parts of cold water, more soluble in warm water, and readily soluble in all organic solvents except petroleum benzin, in which it is soluble, but from which it crystallizes in feathery aggregations. On prolonged keeping it is prone to undergo decomposition, but it keeps permanently in alcoholic solution. It volatilizes gradually at ordinary temperature and readily with steam.

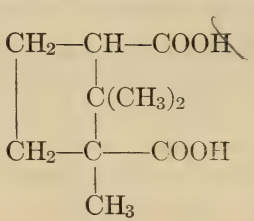
Oxycamphor, being decomposed on prolonged exposure to the air, is marketed only in the form of the 50 per cent alcoholic solution under the name of " oxaphor."

It is used as a substitute for morphin in respiratory disorders.

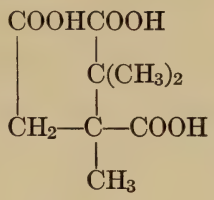
Camphoric Acid

When camphor is treated with nitric acid 1.37 specific gravity, it is converted to camphoric acid, $C_{10}H_{16}O_4$, and on further boiling camphoronic acid, $C_9H_{14}O_6$, results with a very small quantity of isocamphoronic acid.

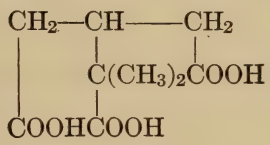
Camphoric acid is dibasic and has the accompanying formula



while camphoronic is tribasic



a stronger chain compound and isocamphoronic is



Camphoric acid is odorless, melts 186°, and at a higher temperature is converted to the anhydride. It is somewhat soluble in water, readily in the organic solvents and oils. It is dextrorotatory $(\alpha)_D+46°$, but a lævo form can be obtained from *l*-camphor and the combination of the two produces the racemic acid, melting 204°. When heated alone or boiled with acetic anhydride, it yields the anhydride which crystallizes from alcohol, melting 217°.

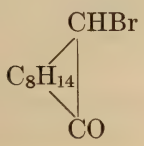
Camphoric acid is an astringent and antiseptic and is used externally in skin diseases, as a gargle alone or mixed with other substances, and for diarrhea, pneumonia, pulmonary affections, calculi, and diseases of the urinary tract.

There are many derivatives of this acid which have been offered as possessing certain medicinal properties not obtainable with the parent substance.

Phenyl hydrogen camphorate, melting.....100°
Thymyl hydrogen camphorate, melting ..... 89°
Guiacyl hydrogen camphorate, melting.....112°
Diguiacyl camphorate, melting.....124°
Eugenyl hydrogen camphorate, melting.....115–116°
Naphthyl hydrogen camphorate, melting.....121–122°

Monobromated Camphor, $C_{10}H_{15}BrO$

This substance is an α-derivative and is α-Bromocamphor



It forms colorless, prismatic needles or scales, having a mild camphoraceous odor. It melts 76°, boils 274° without decomposition, sublimes readily and is volatile with steam. It is insoluble in water but dissolves in the organic solvents and oils and in concentrated sulphuric acid from which it separates unchanged on adding water. It is dextrorotatory $(\alpha)_D + 139°$ in saturated alcoholic solution.

It is decomposed on boiling with silver nitrate solution. On reduction with sodium amalgam in alcoholic solution it yields camphor.

Monobromated camphor will often be found mixed with acetanilid and caffeine, and sometimes with the addition of salicylates, Hyoscyamus and Gelsemium.

Estimation of Monobromated Camphor in Tablets.—W. O. Emery.—Ascertain the weight of twenty or more tablets, reduce to a fine powder, and keep in a small tube or specimen bottle provided with a tightly fitting cork or glass stopper. Weigh out on a metal or glass scoop an amount of the sample equivalent to not less than 100 nor more than 200 mg. of the camphor derivative alleged to be present. Transfer quantitatively to a small (100 mil) round-bottomed flask, with 20 mils of 96 per cent alcohol and 10 mils of water, containing 15 grams of 1 per cent sodium amalgam. Connect flask by means of a rubber stopper with a short vertical reflux, perferably of the Allin or of the worm type. Heat the mixture over a wire gauze just sufficient to cause the liquid to boil gently for a period of not less than thirty minutes. After cooling slightly, wash out the condenser tube, first with 5 mils of alcohol, then 5 mils of water, receiving the washings in the flask below. Remove latter to the steam-bath, heating thereon another hour, or until the evolution of hydrogen has nearly or quite ceased. Toward the latter part of this operation, render the liquid about neutral with a few drops of acetic acid in order to further reduction. Transfer the contents of flask to a separatory funnel preferably of the Squibb type, withdrawing and washing the mercury in a second separatory funnel with at least two 50-mil portions of water. Pass the several aqueous solutions quantitatively through a small filter, collecting the clear filtrate in a suitable beaker. Precipitate with silver nitrate after the addition of about 5 mils of nitric acid, and proceed with the determination of the resulting silver bromide in the usual gravimetric way, employing if available a Gooch crucible in the operation of filtering The weight of the silver bromide multiplied by the factor 1.23 will give the quantity of monobromated camphor originally present in the sample taken for analysis. A control on the amalgam should be run in order to determine whether any correction is necessary with respect to the presence of halogen in material quantity.

This procedure can be used when monobromated camphor occurs alone or in combination with caffein and antipyretics.

Fenchone, $C_{10}H_{16}O$

Fenchone bears a close resemblance to camphor in odor and general properties, but it is a liquid. The *d*-form occurs in fennel and the *l*-form in thuja oils. It melts 5–6°, specific gravity .943–.946, forms an oxime melting 164–165°, but does not react with bisulphite or phenylhydrazine.

Thujone, $C_{10}H_{16}O$

Thujone or tanacetone is a constituent of the oils of thuja, tansy, sage, wormwood, and other species of Artemisia. It has a characteristic odor to which the oils owe in part their aroma, which odor serves a ready means for its identification.

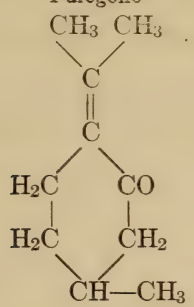
Pure thujone is a colorless, oily liquid, boiling 84.5° at 13 mm., specific gravity .9126 to .916 at 20°, and rotation +68°. It forms a bisulphite compound, an oxime melting 54–55°, and a semicarbazone melting 171–172°.

As thujone is a normal constituent of oil of wormwood its presence would naturally be expected in the beverage known as absinthe, but in neither of the white nor green varieties, as sold in this country previous to the embargo, was the writer able to detect the slightest trace.

Tansy oil is used in female pills, and wormwood oil is an ingredient of a certain type of antiseptic liniment combining the virtues of a number of essential oils in menstruum of acetone or alcohol.

Thuja oil, from Thuja occidentalis, the Arbor Vitæ or White cedar, is used as a tonic and emmenagogue, and as an antiseptic in skin diseases.

Pulegone



Pulegone is the chief constituent of the oil of Mentha pulegium, European pennyroyal, and occurs also to a considerable extent in the oil of Hedeoma pulegioides. These oils, though from botanically different species, are similar in composition and are probably used indiscriminately as " pennyroyal oil " in medicinal products.

Pulegone is a colorless liquid with a sweet peppermint-like odor, boiling 130–131° at 60 mm., specific gravity .9323 at 20° C., rotation +22.89°. Its oxime melts 118–119°, and its semicarbazone at 170°. It forms a bisulphite compound. When heated with water to 250° under pressure, it yields acetone and methyl hexanone, and on oxidation with potassium permanganate acetone and beta-methyl adipinic acid.

Menthone, $C_{10}H_{18}O$

l-menthone occurs in peppermint oil. It is a colorless liquid with a menthol-like odor, boiling 207°, specific gravity .8960 at 20°, rotation −28.18°, oxime melting 59° and semicarbazone melting 184°. It does not unite with bisulphite.

THE CARBOHYDRATES

The carbohydrates are properly considered at this point, as they possess either the properties of ketone alcohols or aldehyde alcohols. They embrace the very important group of substances known as the sugars which are much more interesting to the food than to the drug chemist. The latter, however, will often meet with sugars, as they make up the bulk of some of the most important classes of galencial preparations, including pills, tablets, elixirs, syrups, and powders, and their determination will often be necessary in arriving at the ultimate composition of a sample under investigation.

Cane sugar or sucrose is of common occurrence in all of the above-mentioned classes; commercial glucose which is made up in large part of dextrin and maltose, is used as a builder in pill masses; milk sugar or lactose is present in tablet triturates and in powders as a diluent; maltose will be found in malt extracts; and a mixture of several different carbohydrates is usually found in the many different infant foods.

The carbohydrates with aldehyde or ketone groups form osazones with phenylhydrazine, and these bodies are of value in arriving at the identity of a sugar. It is inadvisable, however, to place too great a dependence on these compounds, because the melting-points are in some instances fairly close to each other, and it is often a question whether one is dealing with an impure osazone of an individual, or the mixed osazones of two different sugars.

For a detailed account of the chemistry of the carbohydrates one should refer to the special books on the subject; but as a guide to the workers the accompanying table has been compiled, and in it will be found a brief summary of the principal distinguishing properties of these substances.

	Common Name	Formula	Products of Hydrolysis	Specific Rotation	Osazone
Dextrose	Grape Sugar or Glucose	$CH_2OH(CHOH)_4CHO$		+52.80	Melts 204–5°
Levulose	Fruit sugar or Fructose	$CH_2OH(CHOH)_3COCH_2OH$		−90.2°	Melts 204°
Sorbose		$C_6H_{12}O_6$		−42°	Melts 164°
Galactose		$CH_2OH(CHOH)_4CHO$		+81°	Melts 196
Arabinose				+105°	Melts 160°
Sucrose	Cane sugar or Saccharose	$C_{12}H_{22}O_{11}$	Dextrose and levulose	+66.50	Non-reducing
Trehalose	Occurs in Manna		Dextrose	+197°	Non-reducing
Lactose	Milk sugar	$C_{12}H_{22}O_{11}$	Dextrose and Galactose	+52.50	
Maltose		$C_{12}H_{22}O_{11}$	2 molecules of Dextrose	+138°	
Starch		$(C_6H_{10}O_5)n$	Acid hydrolysis gives Dextrin and then dextrose Diastase gives Dextrin and Maltose		
Dextrin		$(C_6H_{10}O_5)n$			
Cellulose		$(C_6H_{10}O_5)n$			
Inulin		$C_{36}H_{62}O_{31}$	Levulose	−39.5	

The accompanying method for detecting the nature of the carbohydrates present in mixtures is included.

Identification of Carbohydrates.—(*A*) To 5 mils of a weak solution of the substance add a few drops of 15 per cent alcohol solution of α-naphthol; float this over conc. sulphuric acid, a violet or blue zone at the line of contact indicates a *carbohydrate.*

If the substance is insoluble in water dissolve in 25 per cent sulphuric acid and float over this solution a mixture of water and α-naphthol and observe as above.

(*B*) Shake one gram of the substance with 10 mils water. Decant or filter from any insoluble residue which may be *Starch* or *Cellulose.* Save filtrate.

To insoluble matter in (not on filter paper) add few drops dilute aqueous solution of iodin, blue color shows *starch.*

Filtrate divide into 3 portions α, β, and γ.

α. Divide into 2 portions 1 and 2. To 1 add an equal volume of 94 per cent alcohol; a precipitate indicates *Dextrin.* To 2 on a white slab add a few drops of dilute solution of iodin; blue color indicates cooked starch; reddish-brown indicates *Dextrin.*

β. Boil with Burford's solution of copper acetate; precipitate of Cu_2O indicates either *Dextrose* or *Levulose* or both. Filter and treat

filtrate as follows: Add excess of basic lead acetate solution; filter and to filtrate, add sodium sulphate solution in excess and filter from lead sulphate. To filtrate, which must still be blue (if not add a few drops of copper sulphate solution) add sodium hydroxide to make alkaline and heat to boiling; a red precipitate of Cu_2O indicates *Maltose* or *Lactose* or both. Filter. To filtrate add a few drops sulphuric acid and boil, neutralize with excess sodium hydroxide, add a few drops copper sulphate and heat to boiling; a red precipitate of Cu_2O indicates *Saccharose* (Cane Sugar).

γ. To determine whether Maltose or Lactose are present. Add ammonia in excess, add a few drops of alkaline bismuth solution and set the tube in water at a temperature of about 60° C. *Maltose* solution reduces the bismuth. while *Lactose* does not at this temperature within one-half hour.

To detect *Lactose.* To about 5 mils of strong nitric acid; add .5 gram original substance and warm gently until red fumes begin to come off. Set tube in about 200 mils hot water and allow it to remain there until cold; in a few hours white crystalline mucic acid separates if lactose is present.

Hediosit

Hediosit, $C_7H_{12}O_7$, is the lactone or inner anhydride, of alpha-gluco-heptonic acid, $CH_2OH \cdot (CHOH)_5COOH$.

It is a white, crystalline, odorless powder, with a sweet taste. It is readily soluble in water, slightly soluble in alcohol, and almost insoluble in ether. The aqueous solution is acid toward litmus and does not reduce in Fehling's solution.

If 1 gram of hediosit is heated on a boiling-water bath with 1 mil of water and .5 gram of phenylhydrazine, and a few mils of absolute alcohol added, a light-colored crystalline mass will form, which after recrystallization from dilute alcohol melts at 172° C.

If 1 gram to 2 grams of hediosit weighed into a flask are dissolved in 10 to 20 mils of water by warming and a few drops of phenolphthalein solution added, 9.1 to 9.6 mils of half-normal sodium hydroxide per gram of hediosit taken should be required to neutralize the solution.

If 9 grams of hediosit is dissolved in water to make 100 mils and allowed to stand at the ordinary temperature for twenty-four hours the solution, when polarized at 17° C., should show a specific rotation of about −52° for the sodium line. After neutralization with caustic soda the solution has a slight dextrorotation.

Hediosit is used as a sweetener of the food of diabetic patients.

ANALYSIS OF INFANT FOODS

These products consist usually of carbohydrates and milk solids in varying proportions. They often contain sucrose and sometimes dextrose, but the carbohydrates, which are present in almost all cases are dextrin, maltose, and lactose.

As sold on the market these foods are usually in the form of dry powders, and the analysis in so far as the determination of the content of nitrogen, ash, fat, and moisture are concerned, is the same as for any food product. For fat, the Rose-Gottlieb method is preferable to any other.

Assay for Carbohydrates.—The method of estimating the individual carbohydrates in infant foods was worked out in my laboratory by Mr. T. M. Rector during the course of an extended research which we made on these products.

In preparations containing mixtures of sucrose, maltose, lactose, and dextrin, the sucrose is determined by loss of rotation after inversion with invertase. The dextrin is determined by loss of polarization after precipitation with lead acetate and ammonia. The combined polarization of the sucrose and dextrin is subtracted from the total polarization, giving the polarization of the maltose and lactose. A copper reduction is then run on an aliquot of the solution and the amount of copper reduced by 1 gram of the sample is calculated. From this value and the combined polarization of the maltose and lactose the percentages of these sugars are calculated by a formula.

No claims are made for the availability of this method beyond mixture of carbohydrates of the malted milk type or those prepared synthetically from the same ingredients. Furthermore, the conversion of starch to maltose and dextrin in the preparation of these foods is probably incomplete, and the mixture unquestionably contains dextrin-like substances in various stages of conversion. For this reason the results obtained for dextrin must of necessity be only approximate, and while with known mixtures of the pure ingredients the determination yields theoretical results, in commercial articles the figures obtained would require slight modifications to obtain these actual values.

The specific rotary power of maltose is 138, while the same value for lactose is only 52.5. On the other hand, lactose has a greater reducing power on Fehling's solution than its isomer. Either of these values would serve as a basis to determine the sugars if the total sugar was known, but in the absence of that data a formula, based in the ratios between the polarization and copper-reducing power of the sugars, was devised to determine the ratio of the quantity of one sugar to the other. Then, from the polarization due to the two sugars, their percentages in the mixture was calculated.

To get the best result the constants of the difference carbohydrates should be determined by the analyst himself in order to obviate personal errors as well as possible errors in his polariscope. The constants used are set forth in the following table:

Carbohydrates	Polarization (Ventzke)	Cu_2O per gram
Maltose	207.5	1.277
Lactose	79	1.556
Dextrose	79.2	2.232
Sucrose	100	0
*Dextrin	300	0

* The value used for dextrin was the figure given in the text books. Of several commercial samples of declared purity, none ran over 250°.

The copper-reduction figures were arrived at by using a quantity of sugar that would give about 225 mg. of Cu_2O in a reducing sugar determination conducted according to the method of Munson and Walker. The analytical procedure follows:

Weigh out 32.5 grams of the sample and transfer dry to a 250-mil. graduated flask by means of a wide-stemmed funnel. Add 150 mils of water and digest for at least two hours, shaking frequently. Then add 10 mils each basic lead acetate and alumina cream, shaking flask after each addition, and make up to the mark with water. Filter into a flask through a ribbed filter, keeping the funnel covered with a watch-glass. Add sufficient crystals of normal potassium oxalate to remove excess of lead, allow precipitate to settle and filter through a dry double filter, being sure to guard against loss by evaporation. Preserve 25–50 mils of this solution overnight, to destroy birotation, and polarize in a 200-mm. tube. Multiply reading by 2 and denote product by *a*.

Transfer 50 mils of the solution to a 100-mil volumetric flask, add invertase and keep at from 25–30° C. overnight, in an incubator if necessary. Add 5 mils alumina cream, make up to mark, mix, filter, and polarize in a 200-mm. tube. Multiply reading by 4 and denote product by *b*.

To another aliquot of the original solution of 50 mils contained in a 100-mil volumetric flask, add 25 mils of a 10 per cent solution of lead acetate and 10 mils of strong ammonia. Make up to volume, shake and allow precipitate to settle. Filter through a ribbed filter with the proper precaution to prevent evaporation, and polarize solution immediately in a 200-mm. tube. Multiply reading by 4 and denote product by *c*.

Make up 25 mils of the original solution to 250 mils and run a copper reduction on 25 mils of this solution according to the method of Munson and Walker. Divide the weight of the reduced Cu_2O by .325, the amount of sample represented by the aliquot taken, and denote quotient by *d*.

In most malted milks and similar products this amount will reduce between 200 and 250 mg. of Cu_2O. If the weight is outside these limits, the amount of solution should be adjusted to bring the value within their bounds.

CALCULATIONS OF CARBOHYDRATES

Dextrin

P = the polarization of 26 grams pure dextrin in 200 mm. tube at 20° C. = 300.

Then $$\frac{(a-c)\ 100}{P} = \text{per cent dextrin in sample.}$$

Sucrose

Sucrose is calculated from Clerget's formula, which in this case is:

$$\frac{100\ (a-b)}{142.66 - \frac{T}{2}} = \text{per cent of sucrose in sample} = s$$

Maltose and Lactose

P = polarization of 26 grams of pure maltrose in 200-mm. tube at 20° C. = 207.5.

P' = polarization of 26 grams of pure lactose under these same conditions = 79.

R = grams of Cu_2O reduced by 1 gram of maltose under conditions of method.

R' = grams of Cu_2O reduced by 1 gram of lactose under same conditions.

x = parts of maltose in 100 parts of reducing sugar.

$100 - x$ = parts of lactose in 100 parts of reducing sugar.

T = per cent of total reducing sugar.

S = per cent of sucrose in sample.

Then $$\frac{c-s}{d} = \frac{Px + (100 - x)\ P'}{Rx + (100 - x)\ R'}$$

$$\frac{100\ (c-s)}{Px + P'(100 - x)} = T$$

Tx = per cent maltose.

$T(100 - x)$ = per cent lactose.

If sucrose is absent, this formula is simplified, the first number becoming c/d. By its use any two dextrorotary sugars may be determined, without knowing the total sugars, by substituting the proper values for their polarization and copper reduction.

In the appended table the analyses of some commercial brands of infants foods are shown. A and B are samples of malted milks put out by different firms. The others would be recognized as much advertised infant foods if their names were given.

Sample	*a*	*b*	*c*	*d*	Dextrin	Maltose	Lactose	Sucrose	Dextrose
					Per Cent	Per Cent	Per Cent		Per Cent
A.....	126.4		89.6	.691	12.3	38.3	12.1		
B.....	126.4		88.	.694	12.8	37.1	14.1		
C.....	87.4	58.4	54	.322	11.1	11.1	11.6	21.86	
D.....	149		117.8	.786	10.4	55.5			2.5
E.....	43.2		28.4	.739	4.9	4.2			29.5

Samples A, B, and C contain considerable milk solids, having from 6 to 10 per cent of butter fat besides the milk sugar and casein. Sample C appeared to be a malted milk with cane sugar added. Sample E contained a large amount of unconverted starch besides the soluble carbohydrates.

With the exception of sample E, none of these products gave a blue reaction with iodin. It is probable that the starch was converted entirely to dextrins, and that the dextrins present has a Ventzke value nearer 250 than 300. If this were so, the dextrin value would range higher in the sample than the figures indicate.

The results obtained by this method on mixtures of various sugars are consistent enough for all practical purposes, but as a malt preparation of known composition is impossible to obtain, we have no way of finding out how close the results run on commercial preparations.

The presence of traces of other sugars may in some cases cause the figures to vary slightly from the true amounts, but the results agree very well with what one would expect in such preparations from a general knowledge of their composition.

The results are certainly of more practical use than a meaningless collection of polarization and copper-reduction figures.

Cellulose

Method for Determination of Crude Fiber.—Extract a quantity of the substance representing about 2 grams of the dried material with ether, using any suitable form of extraction apparatus. To this residue in a 500-mil flask add 200 mils of boiling 1.25 per cent solution of sulphuric acid; connect the flask with an inverted condenser, heat at once, boiling gently for thirty minutes Filter through silk, and wash with

hot water until free of acid. Rinse the residue back into the same flask with 200 mils of boiling 1.25 solution of sodium hydroxide, boil at once, and continue the boiling in the same manner as described above for the treatment with acid. Filter through silk and wash with boiling water until the washings are neutral. The residue is then transferred on to a weighed Gooch. This is best accomplished by spreading the silk filter (which is about 18 cm. in diameter, cut and folded like an ordinary filter paper) on a watch-glass slightly larger than the silk filter. The residue is then gently scraped on the weighed Gooch by means of a small spatula. The remaining portion is then rinsed with water, using as little as possible to avoid clogging, suction is then applied, and finally washed with alcohol and ether. Dry to constant weight at 110°; and weigh, after which incinerate completely. The loss in weight is considered crude fiber.

The solution of sulphuric acid and sodium hydroxide are to be made up of the specified strength determined accurately by titration and not merely specific gravity.

CHAPTER XVII

ORGANIC ACIDS

ALIPHATIC SERIES

The organic acids are encountered to a considerable extent in medicinal chemistry. In the aliphatic series we find the monocarboxylic acids of the formic and acetic group of the homologous series $C_nH_{2n+1}COOH$, the oxidation products of the glycols which are hydroxy carboxylic or polycarboxylic, and unsaturated acids of both kinds.

The fatty acids of the general formula $C_nH_{2n+1}COOH$ may be regarded as derivatives of the paraffins, alcohols, or aldehydes.

$$HCH_3 - HCH_2OH - HCHO - HCOOH -$$

The grouping $-C\begin{matrix}=O\\ -OH\end{matrix}$ is known as the carboxyl and is characteristic of them all.

At ordinary temperatures, the lower members of the series are colorless liquids except acetic acid, which solidifies at 16–17°, and are miscible with water, alcohol, and ether in all portions. As the molecular weight increases they become oily in character. The pungency disappears and they are less readily soluble in water. The higher members are waxy or unctuous solids, with a faint odor and insoluble in water. They are all volatile with steam except the higher members, which, however, may be distilled in superheated steam. The specific gravity decreases and the boiling- and melting-points increase as the series is ascended. It should be noted, however, that acids with an odd member of carbon atom melt at a lower temperature than the preceding members containing an even member.

These acids are quite stable and are only oxidized with difficulty. The lower members decompose carbonates, dissolve metals and metallic hydroxides, but these acid properties soon disappear and the higher members are with difficulty recognized as acids by the ordinary tests. The metallic salts of the lower members are soluble in water, but on passing up the series the solubility decreases, and in the case of the higher acids only the alkali salts are soluble. Many of the salts of the higher acids are soluble in ether. The fatty acids react with alcohols, especially in the presence

of dehydrating agents, forming ethereal salts and water. When treated with phosphorus pentachloride they yield acid chlorides, which interact with hydroxy compounds to produce ethereal salts, with ammonia to give amides, and on distillation with an alkali salt of a fatty acid to produce anhydrides.

$$C_2H_5COOH + PCl_5 = C_2H_5COCl + POCl_3 + HCl$$

$$C_2H_5COCl + CH_3OH = C_2H_5COOCH_3 + HCl$$

$$C_2H_5COCl + NH_3 = CH_3CONH_2 + HCl$$

$$C_2H_5COCl + C_2H_5COOH = (C_2H_5CO)_2O + KCl$$

The organic acids and their derivatives will be encountered in a large percentage of the mixtures analyzed by the chemist in this line of work. Often they are subsidiary products to which no attention need be paid, again the crucial feature of an analyis will depend upon their accurate identification and determination, either as a measure of some parent product of which they are a part, or as a measure of their therapeutic efficiency, and still again their influence as contaminating features in the determination of other substances must be considered.

In the aliphatic series the acids which are used for their medicinal properties include formic, valerianic, agaricic, citric, tartaric, lactic, angelic, and succinic, and to a lesser extent acetic, oleic, and stearic. In the aromatic series benzoic, salicylic, and phenolsulphonic acids and their derivatives make up an appalling list of medicinal agents.

Allusion has already been made to the influence of volatile acids on alcohol determinations. The identification of some of the acids will often give valuable evidence as to the presence of certain drugs; angelic acid will indicate angelica root, valerianic acid may denote that valerian has been employed, and benzoic and cinnamic acids often will lead to the discovery of the aromatic balsams. Again the presence of aliphatic acids furnishes additional evidence regarding the use of specific drugs in complex mixtures, for instance the simultaneous discovery of the Sanguinaria alkaloids, and a relatively large amount of acetic acid will indicate that fluid extract of Sanguinaria was one of the components of the mixture.

The acids play an extremely important part in the identification of fats and oils, and in mixtures where the ordinary constants of the oils have become modified or rendered doubtful, the separation of the fatty acids is the only means of identifying the original product. Sometimes it will be necessary to convert the mixed acids into volatile esters, fractionate the mixture and then reform the acids. By this means more has been

accomplished in clearing up the chemistry of cod-liver oil than by any other method.

One general observation regarding the work of the analytical chemist in detecting organic acids may not be amiss at this point. In identifying the acids by color and precipitation tests it is always advisable to convert the suspected individual into a neutral stable salt and to work with an aqueous solution of the latter. For instance, it is stated that benzoic acid will give a flesh-colored precipitate with ferric chloride, but the analyst will usually be disappointed if he attempts to get this reaction by adding ferric chloride to a residue or an aqueous solution of the free acid. But if he adds sufficient dilute ammonia to dissolve the free acid and then evaporates the excess, the aqueous solution will give a copious precipitate of the characteristic salt.

Formic Acid, H·COOH

Formic acid is a colorless, hygroscopic liquid at ordinary temperatures, Specific gravity 1.241 at 0° C., it melts at 8° and boils at 101°. It has a pungent, irritating odor, is very caustic, blistering the skin, and is miscible with alcohol, water, ether, and glycerin. It is acid to litmus, decomposes carbonates, and forms well-defined salts. In some of its reactions it resembles the aldehydes, it reduces ammoniacal silver oxide with evolution of carbon dioxide. When mixed with concentrated sulphuric acid it is rapidly decomposed into carbon monoxide and water, this reaction distinguishing it sharply from the other acids of the aliphatic series. All metallic formates have the same property. Formic acid and formates reduce mercuric chloride to mercurous chloride, and this property is available for their determination. On adding magnesium ribbon to formic acid, hydrogen is evolved and the acid is reduced to formaldehyde, which can be recognized by the morphin sulphuric acid reaction.

Formic acid can be removed completely from an aqueous solution by distillation, but like hydrochloric acid it forms a definite hydrate which has a definite distillation point, and can never be completely separated from water by distillation.

As ordinarily used it will be found in 25 per cent solution and the acid content can be determined by direct titration with normal acid.

Formic acid is the essential ingredient of the treatment for rheumatism known as the "bee sting" remedy. It is also used as an antiseptic, diuretic, and tonic, but it is too irritating for general use. Sodium formate is employed for the purposes above mentioned, and also hypodermically in surgical tuberculosis. It is sometimes dispensed with Adonis vernalis (false hellebore) for pneumonia.

The metallic formates are all soluble in water, but the lead and silver

salts are only moderately soluble; they are all decomposed by warm concentrated sulphuric acid with evolution of carbon monoxide, and by dilute acids yielding formic acid. The alkali formates are deliquescent and when heated to 250° they are converted to oxalates with evolution of hydrogen. When ammonium formate is strongly heated, it is first converted into formamide and then to hydrogen cyanide.

$$HCOONH_4 = H \cdot CONH_2 + H_2O$$

$$HCONH_2 = HCN + H_2O$$

Silver formate is precipitated in colorless crystals on adding silver nitrate to a concentrated solution of alkali formate, but it is unstable and darkens quickly.

The detection of formic acid or a formate is accomplished by adding a slight excess of phosphoric acid to the suspected sample and distilling with steam, the distillate being collected in a receiver containing water and barium carbonate. The distillate is then evaporated to drive off any volatile constituents, aldehydes, etc., diluted with water and filtered. Portions of the filtrate are then tested with ammoniacal silver oxide and mercuric chloride for the characteristic reductions, and another portion evaporated to dryness in a test-tube and warmed very gently with concentrated sulphuric acid and the escaping gas tested with a flame; carbon monoxide will ignite and burn at the mouth of the tube.

The detection and determination of formates will sometimes be of moment in the identification of chloral.

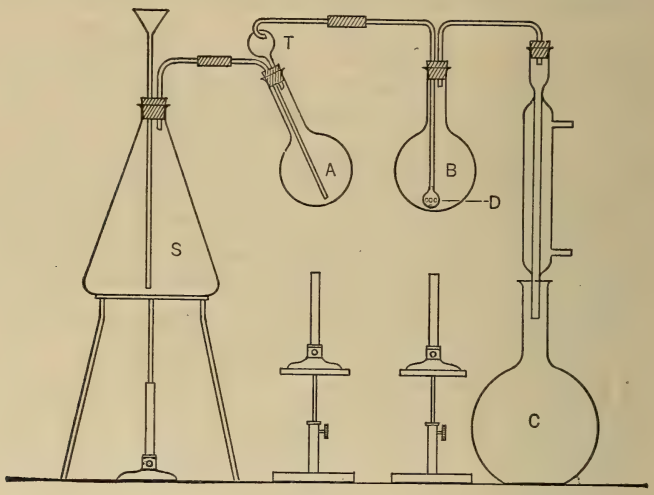
For the determination of formic acid in fruit juices Seeker has modified Finkes method slightly. The results obtained are accurate and the procedure can be used with medicinal products.

In the case of free formic acid this method can be used without modification, but if the qualitative examination indicated a formate, phosphoric acid should be substituted for tartaric.

The apparatus required consists of a steam generator *S*, a 300-mil flask *A* in which the sample is placed, a 500-mil flask *B*, containing a suspension of barium carbonate, a spray trap *T*, a condenser, and a 1-liter graduated flask *C*. The tip of the tube *D*, leading into *B*, consists of a bulb containing a number of small holes to break the vapor into small bubbles.

For thin liquids like fruit juices, use 50 mils. For heavy liquids and semi-solids like sirups and jams, use 50 grams diluted with 50 mils of water. Place the sample in the flask *A*, add 1 gram of tartaric acid, and connect as shown, the flask *B* having been charged previously with a suspension of 2 grams of barium carbonate in 100 mils of water. If much acetic acid is present, sufficient barium carbonate must be used

so that at least 1 gram remains at the end of the operation. Heat the contents of flasks *A* and *B* to boiling and distill with steam from the generator *S*, the vapor passing first through the sample in flask *A*, then through the boiling suspension of barium carbonate in *B*, after which it is condensed, and measured in the graduated flask *C*. Continue the distillation until 1 liter of distillate is collected, maintaining the volume of the liquids in the flasks *A* and *B* as nearly constant as possible by heating with small Bunsen flames, and avoiding charring of the sample in the flask *A*. After 1 liter of distillate has been collected, disconnect the apparatus and filter the contents of flask *B* while hot, washing the barium carbonate with a little hot water. The filtrate and washings should now measure about



150 mils. If not they should be boiled down to that volume. Then add 10 mils of the sodium acetate, 2 mils of 10 per cent hydrochloric acid, and 25 mils of the mercuric chloride reagent. Mix thoroughly and immerse the container in boiling water-bath or steam-bath for two hours. Then filter on a tared Gooch, wash the precipitate thoroughly with cold water and finally with a little alcohol. Dry in a boiling water oven for thirty minutes, cool, weigh, and calculate the weight of formic acid present by multiplying the weight of the precipitate by .0975. If the weight of mercurous chloride obtained exceeds 1.5 grams, the determination must be repeated, using more mercuric chloride reagent or a smaller amount of sample. A blank test should be conducted with each new lot of reagents employed in the reduction, using 150 mils of water, 1 mil of 10 per cent barium chloride solution, 2 mils 10 per cent hydrochloric acid, 10 mils of the sodium acetate, and 25 mils of the mercuric chloride reagent, heating the mixture in a boiling water-bath or steam-bath for two hours. The weight of mercurous

chloride obtained in this blank test must be deducted from that obtained in the regular determination.

Acetic Acid, CH_3COOH

Acetic acid is the bane of the analyst in determining alcohol in drug mixtures. The writer has found it consistently in almost every alcoholic distillate, and as nobody has ever investigated the extent of its influence on the specific gravity, it has to be eliminated before an accurate determination of the alcoholic content can be assured. It is probable that in a great many instances its influence is negligible.

Besides occurring as an oxidation product of alcohol, acetic acid occurs in drug products to a large extent as a vehicle; as a medicine pure and simple, the chief employment of glacial acetic acid is as a vesicatory and for removing warts and corns. It is sometimes used as a substitute for cantharides where a speedy blister is desired.

Acetic acid is employed in the preparation of pharmaceutical products known as vinegars, of which the most important include cantharides, ipecac, opium, squills, Colchicum, Lobelia, Sanguinaria, and the aromatic vinegar consisting of several aromatic oils in alcohol and dilute acetic acid. Acetic acid also occurs in fluid extract of ergot, Nux Vomica, and Sanguinaria.

The dilute acid is used as an excitant in syncope, asphyxia, and headache, where the vapors are applied to the nostrils. Camphorated acetic acid is an old remedy composed of camphor, alcohol, and dilute acetic acid. It is recommended in fainting and nervous debility.

Pure, anhydrous acetic acid is a crystalline solid, melting $16 \cdot 5°$, boiling at $118°$, with a pungent, penetrating odor and a burning action on the skin. It is inflammable when near its boiling-point and burns with a feebly luminous flame. It is hygroscopic, miscible with alcohol, water, and ether, is an excellent solvent for many organic substances, and for certain inorganic elements as sulphur and iodin which do not dissolve in water. It is not removed from its aqueous solution by immiscible solvents, and by this means it may be separated from many of the higher acids of the same series, and from the aromatic acids with the exception of phenolsulphonic. It is a fairly strong acid, dissolving certain metals and metallic oxides, but differs from formic acid in possessing no reducing properties and being stable towards sulphuric acid.

On neutralizing acetic acid with sodium hydroxide and then warming the solution with a little sulphuric acid and alcohol, ethyl acetate is formed and is readily recognized by its characteristic fruity odor. On adding ferric chloride not in excess to free acetic acid a deep-red color soon appears which does not disappear on boiling nor yield a precipitate. If the acid

has been neutralized with sodium hydroxide, or the suspected sample is an acetate the same deep-red color is obtained, and on boiling, a heavy deposit of basic ferric acetate results. The red color is destroyed by hydrochloric or sulphuric acids, differing from that given by meconic acid, and it is not soluble in ether as is the case with thiocyanates. Formic acid will give a red color, but it has other well-marked reactions differing entirely from those of acetic acid, and is readily differentiated. Citric and tartaric acids and their salts give only a yellow color with ferric chloride, but with Rochelle salts a red color develops on long standing.

Chlorine, bromin, chromic acid, etc., convert formic acid into carbon dioxide, but they do not affect acetic acid in this way. Chromic acid is without action on pure acetic acid.

The normal acetates are all well-defined salts. The silver salt is sparingly soluble in water and is precipitated in colorless crystals on adding silver nitrate to a concentrated neutral solution of an acetate. The double salts of copper acetate and arsenite are insoluble and have a wide use as insecticides.

Lead acetate is used as an astringent, styptic, and sedative. It is given for diarrhea, dysentery, and internal hemmorhages, in gonorrheal injections, externally as an astringent eye lotion, and as a remedy for poison ivy. It will often be found in conjunction with opium and camphor in diarrhea mixtures, and with zinc acetate or sulphate and the Hydrastis alkaloids in astringent washes.

An aqueous solution of acetic acid may be tested for the presence of the acid by neutralizing a portion with sodium hydroxide, concentrating and then warming with alcohol and sulphuric acid when the characteristic odor of the ethyl acetate is evolved. It will also respond to the test with ferric chloride. In such simple mixtures the acetic acid may be determined by titration with standard alkali.

In complex mixtures the acetic acid should be distilled off into an aqueous suspension of barium carbonate, and the distillate concentrated and then filtered, the filtrate being tested as above. Acetic acid in combination as acetate may be detected by distilling the mixture with steam in the presence of phosphoric acid, running the distillate through barium carbonate as described under the determination of formic acid and finally filtering off the solution of barium acetate and testing as above.

Assay of Acetates.—The assaying of acetates may be accomplished by distillation in the presence of sulphuric or phosphoric acid. The sample is transferred to a distillation apparatus fitted up for steam distillation, using a spray trap to connect the distillation flask with the condenser. The solution is made up to 100 mils and 5 mils of concentrated sulphuric acid added. Distillation is continued until about 600 mils of liquid have been collected, and the acid residue reduced to about 20 mils. The dis-

tillate is titrated with N/10 alkali, using phenolphthalein as an indicator, finally boiling the liquid until a faint pink color persists. It is well to add a quantity of distilled water to the acid residue and distill over a fraction of 100 mils to be sure that all of the acetic acid has been expelled. Correct the result by a blank determination.

Formic acid can be separated from acetic by forming the lead or magnesium salts, concentrating and adding excess of alcohol in which the formates are insoluble, while the acetates remain in solution.

Acetic acid gives three chlor, three bromo, and three iodo- derivatives, one of which, trichloracetic acid is employed to some extent as medicine and has already been described, see page 593.

Acetic anhydride is prepared by heating anhydrous sodium acetate with phosphorus oxychloride.

$$4\ CH_3COONa + POCl_3 = 2(CH_3CO)_2O + NaPO_3 + 3NaCl$$

It is a mobile liquid boiling at 137°, with an unpleasant irritating odor. It does not mix with water but is soon decomposed, especially on warming, giving two molecules of acetic acid.

The Valerianic Acids

The Valerianic acids need no other characteristic than their odor to assure the analyst of their presence. This odor is characteristic and is a conclusive test. Its penetrating and clinging properties are familiar to all who have had any experience in drug analysis. Valerianic acid or its esters are present in the roots of valerian, angelica and sumbul and in Viburnum bark, and the isolation of the acid from liquid mixtures containing drug extractive, points to the presence of these drugs. Angelica and sumbul contain in addition angelic acid, which has well-defined and characteristic properties.

There are four possible isomerides of the molecular formula $C_5H_{10}O_2$, but isovalerianic or isopropylacetic acid $(CH_3)_2CHCH_2COOH$, and active valerianic or methyl ethyl acetic acid, $\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!CHCOOH$ are the most important. The former when pure is a transparent colorless oily liquid, boiling 175°, miscible in all proportions with alcohol, ether, and chloroform and fairly soluble in water from which it may be separated by adding calcium chloride. It is the principal valerianic acid obtained from the drugs and is also prepared from amyl alcohol. It is used in nervous affections, hysteria, and mania. Active valerianic acid is the principal valerianic acid obtained from angelica. It boils 172° $(\alpha)_D$ −17.85.

The valerianates are used to a considerable extent in medicine, especially the salts of iron, zinc, quinin, and strychnin. These salts are employed as sedatives in elixirs and liquid products. They are more or less unstable, and are acid in reaction, and give off a strong odor of the acid. The acid is readily separated on warming with mineral acid and distilling with steam.

Isovalerianic acid forms a hydrate, $C_5H_{10}O_2H_2O$, boiling 165°. Isovalerianates are decomposed by acetic, tartaric, and citric acids. Zinc valerianate is distinguished from zinc caproate by being soluble in water.

Nonylic Acids

Pelargonic or normal nonylic acid, $C_8H_{17}COOH$, is formed when essential oil of rue is oxidized by nitric acid. It is an oily liquid with a faint odor melting 12°, boiling 245°, insoluble in water. The palargonates with the exception of the alkalies are insoluble in water.

Myristic Acid

Myristic acid, $C_{13}H_{27}COOH$, melts 54°. It occurs in oil of nutmeg, probably in combination.

Palmitic Acid

Palmitic acid, $C_{15}H_{31}COOH$, occurs in palm oil as a glyceride, as an ethereal salt, cetyl palmitate, in spermaceti, and as myricyl palmitate in beeswax. It is also found combined in other fats and waxes of lesser importance, and in the complex resinous constituents of many drugs. Palmitin, the triglyceride, occurs in the most liquid fats such as palm and cocoanut oil, as well as in butter and human fat.

The pure acid is a colorless waxy substance, melting at 62° C., soluble in alcohol and ether, insoluble in water and decomposing on distillation, except in the presence of steam. The alkali palmitates are soluble in water and occur in soap. The salts of the other bases are insoluble in water, and even the alkali salts are thrown out of acid solution on adding sodium chloride.

Margaric Acid, $C_{16}H_{33}COOH$

The acid is obtained by boiling cetyl cyanide with an alkali. It was formerly supposed to exist as a glyceride in natural fats, but subsequent researches seem to prove that the substance obtained at that time was a mixture of palmitic and stearic acid. It is a crystalline waxy substance, melting 59–60° C.

Stearic Acid

Stearic acid, $C_{17}H_{35}COOH$, occurs as a glyceride in many animal fats, especially suet, and in the solid fats generally. The pure acid is a white crystalline solid, melting at 69° and resembling palmitic acid in its chemical and physical properties. Sodium and potassium stearates are soluble in water to a clear solution, but on adding a large excess of solvent, the acid stearates are deposited in scaly crystals.

Dioxystearic, $C_{17}H_{33}(OH)_2COOH$, melting 35°, is obtained by treating dibromisoleic acid with silver oxide.

Isotrioxystearic, $C_{17}H_{32}(OH)_3COOH$, melting 111°, is formed on oxidizing castor oil with alkaline permanganate.

Tetraoxystearic or sativic, $C_{17}H_{31}(OH)_4COOH$, melting 159–161°, is formed on oxidizing linoleic acid with alkaline permanganate.

Arachidic Acid, $C_{19}H_{39}COOH$

The acid in the form of a glyceride is one of the important constituents of peanut oil. Its separation and identification is a problem familiar to the food chemist, as its presence is used in drawing conclusions as to the adulteration of other edible oils, especially olive oil. As it occurs as a glyceride in other oils and to some extent in olive, its occurrence is not necessarily a conclusion that peanut oil has been used as an adulterant.

The pure acid occurs in small shiny plates of a pearly luster, melting 75° C.

Behenic Acid, $C_{21}H_{43}COOH$

Behenic acid is found in the oil expressed from the seeds of Moringa oleifera (oil of ben). It melts 80–82° and solidifies 79–76°. It has been prepared synthetically from erucic acid and then melts 83–84°. This acid is of interest as it is used in the preparation of a series of organic arsenic compounds for which medicinal virtures are claimed.

The salts of the bromo and iodo derivatives of behenic acid prepared from erucic acid are used as remedies in which it is desired to obtain the effects of bromin or iodin.

Sabromin, Dibrombehenate of Calcium, $(C_{21}H_{41}Br_2COOH)_2Ca$

Sabromin is a colorless, odorless, and tasteless powder claimed to contain about 29 per cent bromin and about 3.8 per cent calcium. It is insoluble in water and alcohol, soluble in ether, acetone, benzol, ligroin and tetrachloride of carbon. On heating on platinum foil it is decomposed with liberation of bromin.

Sajodin, Monoiodobehenate of Calcium, $(C_{21}H_{42}ICOO)_2Ca$

Sajodin is a colorless, odorless and tasteless powder, insoluble in water. On heating it generates an abundance of iodin vapor; on exposure to light the superficial portion becomes yellow without material decomposition.

It should contain 26 per cent of iodin and 4.1 per cent of calcium.

It is used for the same purposes as potassium iodide.

Ferro-sarjodin

Basic ferric iodobehenate. Ferro-sajodin has the approximate formula $(C_{21}H_{42}ICOO)_2(OH)Fe$, and containing at least 5 per cent of iron and at least 24 per cent of iodin.

It is a reddish-brown powder, unctuous to the touch, insoluble in water; soluble in chloroform and ether, on heating it melts to a brownish-black liquid, which emits an abundance of iodin vapors.

It is indicated in conditions in which iron and iodin are employed, such as anemia, rickets, syphilis, chronic bronchitis, arteriosclerosis, etc.

Cerotic Acid

Cerotic acid, $C_{26}H_{53}COOH$, occurs in Chinese wax as ceryl cerotate an ethereal salt corresponding with cerylpalmitate in spermaceti and in beeswax, and in the free state in the Carnauba wax. It no doubt occurs in many other waxes whose compositions have not been investigated.

It is a white powdery substance when pure, melting 78–82° C.

SOAPS

The chemistry of soap is intimately connected with that of palmitic and stearic acids.

Soluble soaps consist of sodium or potassium or ammonium palmitate or stearate or oleate, or mixtures of these, containing more or less water, often perfumed and medicated, and sometimes entirely liquid and containing ether or some solvent. The soaps with which we are especially interested are called medicated soaps.

The official soap of the Pharmacopœia is an olive oil soda soap in which of course the oleates predominate. Large quantities of soap are made from palm and cocoanut oils, stearin, and lard oil. Soaps contain varying amounts of water, the better grades little and the cheaper grades most. After the amount of water reaches a certain percentage, about 30 per cent, the soap will float.

Medicated soaps are offered as remedies for skin diseases, as antiseptic washes, and for introducing oxygen into the system. The latter feature has come into vogue during very recent years in the so-called " peroxide " soaps.

If a soap contains sufficient medicament to be of value from a therapeutic standpoint, the essential ingredients can be readily detected. The sample should be dissolved in water or digested with water until disintegrated, and then treated with an excess of dilute sulphuric acid, and poured into a separator and shaken with ether. The metallic bases and any alkaloids which might be present will be in the aqueous solution, and the fatty acids, phenols, cresols, iodoform, thymol diiodide and similar substances will be dissolved in the ether, and any bran, siliceous material and the like will remain undissolved. The acid aqueous solution is then drawn off, and a portion tested with a crystal of potassium chromate and a little absolute ether, and if peroxide is present a deep blue color will be imparted to the ether. The balance of the acid solution is then treated with excess of alkali and shaken with ether to remove organic bases which should be sought for after evaporating the ether, and the alkaline liquid treated with excess of hydrochloric acid and tested for metals, especially mercury and zinc, and also for borates.

The ether solution containing the fatty acids, etc., should then be shaken with dilute sodium hydroxide, which will remove the acids and phenolic bodies, and then separated and the ether filtered, leaving the bran behind, evaporated and examined for iodoform, thymol diiodide and petrolatum. The alkaline liquid is then treated with excess of hydrochloric acid and shaken with ether, the solvent filtered and cautiously evaporated and the residue treated with hot water, the water separated and filtered and examined for phenolic bodies, by noting the color given by ferric chloride, and precipitating with bromin water. The bromin precipitate can be purified and its melting-point determined.

After a preliminary qualitative test, a quantitative estimation can be made along the same lines indicated. Mercury may be precipitated as sulphide and weighed, and zinc as sulphide, filtered, redissolved, and precipitated as carbonate, ignited, and weighed as oxide.

As a general thing it can be said of the soaps now in use, that the amount of metallic ingredients will be sufficient to give a good quantitative test, but that the phenolic bodies are only in minute quantities.

Some soaps claim iodin as an ingredient, but it is usually in such small quantity that its detection is difficult, and its determination of little real value.

Peroxide soaps are much in vogue, and if more than a trace of peroxide is present it can readily be detected by the method outlined above. If the sample does not respond to this reaction another test should be applied

with titanium potassium oxalate and any darkening noted. This latter reaction must, however, be considered with caution, because it has not yet been determined whether other substances present might give this same coloration.

Soap is employed medicinally as a laxative, antacid, and antilithic and is often combined with rhubarb in remedies for dyspepsia, constipation, and biliousness. It has been recommended for urinary calculi, but is of doubtful value, though it should be looked for in such preparations. It is often found in liniments combined with opium, camphor, and potassium iodide. It is one of the chief constituents of the official soap liniment known as " liquid opodeldoc."

Lead soap, which is really lead oleate, is known as lead plaster, and lime soap, lime liniment, or Carron oil, are well-known medicinal agents. Ammonia liniment consisting of olive oil partially or wholly saponified by ammonia in alcohol, is used for croup and inflammatory conditions of the throat.

Solid opodeldoc is stearin sodium soap containing alcohol.

Assay of Soap.—The moisture in soap is determined by dissolving about .5 gram of the sample accurately weighed in 10 mils of alcohol, and evaporating to dryness in tared dish containing 1 gram clean sand, which has been previously heated to 110°. The residue is dried at 110° to constant weight.

Insoluble impurities and free alkalinity are determined by dissolving 10 grams in 100 mils of alcohol and filtering any undissolved residue into a tared Gooch and washing with hot alcohol. The residue is dried and weighed, and represents chloride, carbonate, and silica. It is then washed with boiling water, which dissolves the chloride and carbonate, and the silica can then be dried and weighed. Free alkalinity can be determined in the alcoholic filtrate by titrating with standard acid using phenolphthalein.

Fatty acids and total combined alkali metals are determined by using an alcoholic solution of the soap obtained as above. The alcohol is driven off over the steam-bath, the residue taken up with water, transferred to a separator, acidulated with sulphuric acid, and shaken with ether. The acid liquid is drawn off through a filter into a platinum dish, the filter washed, the solution evaporated to dryness and carefully ignited to constant weight as sulphate of the alkali metal present. The fatty acids are in the ether layer and may be estimated by evaporating the ether in a tared dish weighing the residue.

Assay of Soap Liniment.—*Specific Gravity.*—Determine this value at any convenient temperature.

Camphor.—Determine rotation in 200-mil tube, using sugar scale. Standard soap liniment averages about 65–70 per cent alcohol, and a solu-

tion of camphor in alcohol of this strength in the proportion of 4.5 grams of 100 mils, rotates the scale about 9.5°.

Alcohol.—Fifty mils are transferred to a distilling flask, diluted to 200 mils, and 100 mils distilled over. This distillate is transferred to a separator, saturated with sodium chloride, and shaken out with low-boiling petroleum ether to remove the volatile oils. The balance of the determination follows the directions given for determining alcohol in the chapter on general methods. Collect the pure distillate in a 100-mil flask. The percentage of alcohol corresponding to the specific gravity will be half that present in the sample.

Fatty Acids and Alkali (Anhydrous Soap).—Evaporate the alcohol from a 50-mil sample. Transfer to separator, using water, and add a slight excess of dilute sulphuric acid. Shake out with ether, collecting ether extractions in another separator, washing, and finally evaporating to dryness in a tared beaker, the weight being the *fatty acids.*

The acid liquid is filtered into a platinum dish, the filter washed, the solution evaporated to dryness, cautiously ignited and weighed as sulphate of the alkali present. By calculating the alkali to oxide (Na_2O or K_2O) and adding the result to the weight of the fatty acid, the final figures will be the quantity of anhydrous soap present. Good soap liniments will average slightly over 6 per cent anhydrous sodium soap.

SEPARATION OF ACIDS OF ACETIC SERIES

The acids of this series can be separated from each other in several ways. The lower members can be separated from the middle and higher acids by treating an aqueous mixture with calcium chloride and shaking out with ether. By this procedure all of the acids except formic and acetic will dissolve in the ether, and on drawing off the aqueous solution and washing the ether with a solution of calcium chloride, formic, and acetic will be found in the aqueous portion. They can be distilled off with steam from the calcium chloride after acidulating with tartaric acid and separated from each other by taking advantage of the difference in the solubilities of their lead salts in alcohol.

The ether solution should then be evaporated and the middle members separated from the higher by washing out the residue with hot water. These acids, which are for the most part volatile, can then be separated by the method of partial saturation. The mixture is divided equally and one of the portions exactly neutralized with sodium hydroxide; the other half is then added and the whole distilled. As the acid strength diminishes with the increase in the number of carbon atoms, the lower acid in the mixture will displace the higher. For instance, butyric acid will dis-

place valerianic acid, and if the mixture contained equal quantities of the two, the distillate would contain only valeric acid and the residue sodium butyrate. If the valerianic acid predominated, the aqueous solution would contain both butyrate and valerianate, and when distilled in the presence of phosphoric acid, would yield a fresh mixture of the acids which can be treated in the same way. If butyric acid were in greater amount the distillate would contain both acids and must be again treated by partial saturation as before.

The non-volatile acids may be separated by the fractional precipitation of their lead, barium or magnesium salts, the insolubility of which increases with the number of carbon atoms. The acid mixture is dissolved in alcohol and partially precipitated by an alcoholic solution of lead, barium, or magnesium acetate, the precipitate consisting largely of the acid of highest molecular weight. It is filtered and another precipitate obtained from the filtrate, which will consist of acids lower in carbon and so on. Each precipitate is then decomposed by hydrochloric acid and the new mixture of acids subjected to the same treatment until the separated acids yield constant melting-points.

Another procedure for separating and determining the identity of the higher fatty acids depends on their conversion to their methyl esters and fractionating. Bull adopted this procedure when working with the acids of cod-liver oil.

DETECTION AND ESTIMATION OF ACIDS OF ACETIC SERIES WHEN IN ADMIXTURE

The free acids obtained by distillation are saturated by barium carbonate or by the cautious addition of baryta water (using phenolphthalein to indicate the point of neutrality), the latter method being preferable for the higher numbers of the series. In this way, neutral barium salts are formed, which may be obtained in the anhydrous state by evaporating off the water and drying the residue at 130°. These barium salts contain percentages of barium dependent on the atomic weights of the fatty acids present. On moistening the residue with sulphuric acid and then igniting, an amount of barium sulphate is obtained proportional to the percentage of barium contained in the salt of the fatty acid present. Instead of weighing the barium sulphate, a standard solution of baryta water may be employed and the weight of barium (or its equivalent of barium sulphate) calculated from the volume of solution employed. This method also serves as a useful check on the determination of the weight of barium sulphate. The following table shows the proportions of barium contained in, and of barium sulphate producible from the barium salts of the lower acids of the acetic series:

Name of Salt	Barium, Per Cent	Barium Sulphate, Per Cent
Barium formate	70.25	119.47
Barium acetate	53.73	91.37
Barium propionate	48.41	82.13
Barium butyrate	44.05	74.91
Barium valerianate	40.41	68.73
Barium caproate	37.33	63.48
Barium oenanthylate	34.68	58.98
Barium caprylate	32.39	55.08
Barium pelargonate	30.38	51.66
Barium caprate	28.60	48.64

From this table it will be seen that the pure barium salts of the lower acids of the acetic acids can very readily be distinguished from each other by estimating the percentage of barium contained in them. In the case of mixtures of two acids the identity of which is established, the proportions in which the two are present may be calculated from the following formula, in which x is the percentage of barium salt of the lower fatty acid in the mixed barium salts obtained; P, the percentage of barium sulphate yielded by the mixed barium salts on treatment with sulphuric acids; B, the percentage of the same theoretically obtainable from the pure salt of the lower fatty acid; and b, the percentage of the same, theoretically obtainable from the pure salt of the higher fatty acid. Then

$$Bx = 100P + bx - 100b.$$

For example, suppose a mixed barium salt known or assumed to consist of acetate and valerate to have yielded a precipitate of barium sulphate equivalent 78.45 per cent of the weight taken, when treated with sulphuric acid and ignited. Then, by the above formula,

$$91.37x = 7845 + 68.73x - 6873,$$

therefore $22.64x = 972,$

and $x = 42.93.$

Hence the mixed barium salt consisted of 42.93 of barium acetate, and 57.07 of barium valerate. From these data and the weight of mixed barium salt found, the actual amounts of acetic and valeric acid may be calculated.

ACIDS OF THE ACRYLIC OR OLEIC SERIES, $C_nH_{2n-1}COOH$

The acids of this series are unsaturated and therefore show marked differences from those of the preceding series, but all reactions affecting

the carboxyl group are analogous. They combine directly with two atoms of bromin to form dibrom substitution products of the acids of the acetic series, thus oleic acid gives dibrom-stearic acid. When these dibrom acids are boiled with alcoholic potash they yield either monobrom substitution products of the acrylic series, or both bromin atoms are removed as hydrobromic acid and a new acid of the next series (propiolic) is produced.

The higher members of this series are reduced to saturated acids by hydriodic acid.

These acids on fusion with potassium hydroxide are converted to potassium salts of two members of the acetic series, the acids produced depending on the position of the double bond; thus acrylic acid yields acetate and formate, and solid crotonic acid two molecules of acetate.

The higher members are converted into crystalline isomerides by the action of nitrous anhydride.

The Crotonic Acids

Solid crotonic acid, $CH_3CH=CHCOOH$, forms needles melting 72°, boiling 189° C. It is somewhat soluble in water, and has an odor like butyric acid, into which it is converted by nascent hydrogen.

Liquid crotonic acid is apparently a stereoisomeride of the former, into which t is converted by heating to 180° C. The boiling-point is given at 172°. It is claimed to be present in croton oil.

Methyl acrylic acid, $CH_2=C(CH_3)COOH$, has been reported as occurring as an ester in oil of chamomile. It melts 16° and boils 160° C.

Angelic Acid, $CH_2=CHCH(CH_3)COOH$

This acid and its isomeride, tiglic or methyl crotonic acid, are important in our work. The former occurs as an ethereal salt in the oils of cumin and Roman chamomile and probably other species of Anthemis, and in Arnica montana, and also in angelica root. It forms monoclinic prisms or needles of a spicy odor, melting 45°, boiling 185°, soluble in alcohol, ether, and hot water. It may be obtained by boiling an extract of the root with alkali, filtering, acidifying with phosphoric acid, and distilling.

Tiglic acid, $CH_3CH=C(CH_3)COOH$, an isomer of angelic acid, is a liquid, occurs in croton oil, cumin oil, and chamomile, and is also a product of decomposition of some of the Cevadilla alkaloids. It apparently occurs in croton oil as a glyceride. It is obtained from cumin and chamomile oils with angelic acid. It differs markedly from angelic acid in being a vesicant, and will quickly produce blisters.

The identification of angelic acid will not necessarily prove the presence of angelica root in a preparation, but if it is found without the accompanying tiglic acid, which seems to be absent in the drug, but which does occur in chamomile and cumin, the presence of angelica is probable.

Angelic acid may be expected to occur in tonic mixtures, and in some cases the angelica will be apparent by its characteristic odor. It will also be found in liniments and local absorbents and application for ulcers and goiter, where it occurs in some of the tinctures recommended for such ailments, with arnica and chamomile.

OLEIC ACID, $C_{17}H_{33}COOH$

This acid is the most important of the oleic series, and is of interest to us because it is the acid constituent of the salt used to make lead plaster, and is used for making oleates. It occurs as a glyceride in many fats and oils used in ointments and for various other pharmaceutical purposes. It is sometimes used as a medicine in biliary colic.

It is an oily liquid, solidifying at 0°, and melting again at 14° C., soluble in alcohol, ether, and chloroform. Under ordinary conditions it cannot be distilled without decomposition, but with superheated steam it goes over at 250°. On fusion with potassium hydroxide it gives acetate and palmitate. Nitric anhydride converts it into isomeric elaidic acid, which is a solid at ordinary temperature and melts at 45°. This is called the Elaidin test and is often applied to oils. It absorbs oxygen with considerable readiness, becoming darker in color and as recovered from oils as found in commerce, it seldom is in a chemically pure state.

The alkali oleates are soluble in water, and if a large quantity of the solvent is present, insoluble acid oleates are formed. Barium oleate is insoluble in water. The lead salt is soluble in ether, differing markedly in this respect from the lead salts of the saturated acids. This property furnishes a means of separating oleic acid from stearic and palmitic acids. On digesting the mixed acids with litharge for an hour at 100° C., and then treating with ether, the oleate will dissolve together with small quantities of the other lead salts, and on shaking with dilute sulphuric or hydrochloric acid the lead is precipitated and the pure acid recovered from the ethereal solution. It should not be taken for granted that an acid obtained by this procedure is necessarily oleic acid alone, or even oleic acid at all, for the lead salts of many other unsaturated acids occurring in fixed oils have not been investigated as yet.

The oleates are prepared either by treating a metallic oxide or free alkaloid with oleic acid, or by double decomposition of a soluble solution of sodium oleate with a soluble salt of the metal.

HYDROXY AND DIBASIC ACIDS OF THE ALIPATHIC SERIES

These acids may be considered as oxidation products of the glycols, and some of them are extremely important in medicinal chemistry, both from an analytical and therapeutic standpoint They may be divided into four groups.

1. Hydroxy monocarboxylic acids, of which lactic acid is important.
2. Dicarboxylic acids, including oxalic and succinic acids.
3. Hydroxydicarboxylic acids, of which tartaric acid is important.
4. Hydroxytricarboxylic acids, represented by citric acid.

Hydroxy Monocarboxylic Acids

Theoretically the simplest member of the group should be hydroxy formic O·H·COOH, or carbonic acid; the acid is not known in the free state, but as its anhydride, carbon dioxide.

Glycollic or hydroxyacetic acid, $\begin{matrix}CH_2OH\\|\\COOH\end{matrix}$, is obtained by boiling the potassium salt of monochloracetic acid with water.

$$CH_2ClCOOH + HOH = \begin{matrix}CH_2OH\\|\\COOH\end{matrix} + HCl.$$

It is also produced on oxidizing glycol and by treating amido acetic acid with nitrous acid.

Glycollic acid is a crystalline hygroscopic substance, melting 80°, and readily soluble in alcohol, water, and ether. It has both acid and alcoholic properties, neutralizing carbonates and forming salts, oxidizing to the aldehyde acid glyoxalic acid, and on further oxidation to oxalic acid. When the carboxyl group is esterified the hydroxyl may still be displaced by alkali metals and the acetyl group. When heated with sulphuric acid it is decomposed into formaldehyde and formic acid.

Lactic Acids

There are two lactic acids, α-hydroxypropionic or ethylidene lactic acid, $CH_3CHOHCOOH$, and β-hydroxypropionic, ethylene lactic or hydracrylic, $CH_2(OH)CH_2COOH$.

The former exists in three modifications, dextro, lævo, and inactive, and the inactive is known as fermentation lactic acid, the commonly occurring acid, and is formed during the fermentation of sugar, starch, etc., in presence of nitrogenous animal matter, and is present in sour milk.

It will seldom if ever be found in the pure isolated state, but occurs as a thick syrupy aqueous solution, miscible with water, alcohol, and ether, but not with chloroform. It cannot be distilled, and is readily broken up on warming with dilute sulphuric acid, yielding acetaldehyde and formic acid. It functionates as an acid and a secondary alcohol. It forms metallic and ethereal salts, and the salts themselves will react with acetyl chloride with reactions affecting the hydroxyl group; it acts like a secondary alcohol giving α-brom propionic acid with hydrobromic acid, $CH_3CHOHCOOH+HBr=CH_3CHBrCOOH+H_2O$, and propionic acid with hydriodic acid, the α-iodo acid first produced being reduced,

$$CH_3CHICOOH+HI=CH_3CH_2COOH+I_2$$

On oxidation with permanganate it is converted into pyruvic acid, a keto acid.

$$CH_3CHOHCOOH+O=CH_3COCOOH+H_2O -$$

Nitric acid converts lactic acid to oxalic acid, and chromic acid produces acetic acid, carbon dioxide, and water.

Most of the lactates are soluble; the zinc and calcium salts are crystalline and soluble in hot water. It does not give a precipitate with lead acetate. The zinc salt is precipitated when zinc sulphate is added to lactic acid neutralized with ammonia. Salts of the type $CH_3CHOMCOOM$ are known, thus sodium sodio-lactate is prepared by the action of sodium on sodium lactate. The combination of lactates with phosphates known as lacto phosphates, have an extensive use in medicine.

Copper phosphate produces a deep-blue solution but no precipitate. The strength of the commercial acid is about 75 per cent, and when heated to 150° it is largely converted into a substance called concrete lactic acid or lactide, which is probably an anhydride. It has considerable solvent action on calcium phosphate, and is therefore used to remove tartar from the teeth.

Lactic acid can be titrated directly with alkali hydroxides, using phenolphthalein. When lactic acid syrup is evaporated at the ordinary temperature in dry air as in a desiccator, the anhydride and lactide are gradually formed, the same results occur when the acid is heated above 130° C. These substances are nearly insoluble in water, but are reconverted into lactic acid on boiling with water, or when treated with alkali hydroxides. In commercial lactic acid the anhydride commonly runs up to 10 per cent.

Concentrated sulphuric acid does not blacken lactic acid in the cold, and on warming the mixture turns brown with copious evolution of carbon monoxide. When heated with dilute sulphuric acid, acetaldehyde and formic acid are evolved. When distilled with calcium oxide, carbon dioxide and ethyl alcohol are evolved.

Lactic acid gives a lead salt which is soluble in water, and a barium salt soluble in alcohol. Zinc lactate is insoluble in alcohol.

A dilute solution of lactic acid on distillation with sulphuric acid and potassium bichromate yields formic acid and acetaldehyde. If the distillate is conducted through barium carbonate as detailed under the Determination of Formic Acid, the presence of the latter can be detected, and the aldehyde identified in the final distillate.

If a weak solution of the pure acid is heated to 100° with concentrated sulphuric acid for two minutes, portions of the product will give a rose-red color with alcoholic solutions of guaiacol, and an orange-red with alcoholic codein. The color is due to acetaldehyde. Glycollic acid would give formaldehyde and hence different coloration.

Commercial lactic acid is tested for its content of free acid and anhydride by the following methods:

Free Acid.—Twenty grams are diluted to 250 mils and 25 mils of the dilute solution titrated direct, as rapidly as possible in the cold with N/5 alkali, using phenolphthalein. One mil = .0181 gram lactic acid. The end-point is reached when a pink color appears, which remains on stirring.

Anhydride.—Twenty-five mils of the same solution are boiled with a known excess of N/5 alkali for ten minutes, and after adding sufficient N/5 acid to neutralize the alkali, the excess of acid is titrated back with alkali. The difference between the first and second determinations gives the anhydride.

The determinations of lactic acid and lactates in pharmaceutical mixtures is still a problem of research. There are undoubtedly assay methods which give fairly accurate indications of the percentage values of the pure substances, but they are not applicable to mixtures.

Inactive lactic acid can be separated into the two modifications by the difference in solubility of the strychnin or morphin salts, the lævo form being the least soluble.

Dextro or sarcolactic acid occurs in juices of muscular tissue and in certain body excretions. Its anhydride and salts are lævo rotatory. It is almost completely precipitated from its solution by copper sulphate, while inactive lactic acid yields a deep-blue liquid.

The lactic acids give the iodoform reaction.

Ethylene Lactic Acid or Hydracrylic Acid

This acid is also found in meat juices and is distinguished from ethylidene lactic acid in yielding no anhydrides, but acrylic acid and water when heated. When oxidized it yields carbon dioxide and oxalic acid. Its zinc salt is very soluble in water.

Lactic acid is used as a remedy for dyspepsia, diarrhea, diabetes, the

removal of phosphate in the urine, the removal of false membranes as in diphtheria and croup, in tuberculous affections of the mouth and throat, and for removing tartar from the teeth. It is also combined with pepsin, as it is supposed to increase the solvent power of the ferment on food.

Lactic acid is sometimes used in the form of sticks which consist of the acid and menthol held in a gelatin base.

It is largely dispensed in syrups and elixirs, combined with alkali metals and calcium.

The most important salts medically are those of calcium, magnesium, sodium, potassium, and lithium.

Zinc lactate has been employed in epilepsy, and mercury and silver lactates in diseases of the mucous membrane.

Glycerol mono- and di-lactates are used medicinally.

A compound of lactic acid and santalol is prepared by heating the acid and oil of sandalwood at 130–140° for several hours. The product is purified by washing with water, bicarbonate and hydrochloric acid. It is a reddish-brown liquid, insoluble in water, but soluble in organic solvents.

Estimation of Lactic Acid in Lactates.—The method which gives good results in some cases where other methods are either useless or too troublesome, depends upon the oxidation of lactates in sulphuric acid solution, by means of standard potassium bichromate solution, when the following reaction takes place;

$$3C_3H_6O_3+2K_2Cr_2O_7+8H_2SO_4$$
$$=2K_2SO_4+2Cr_2(SO_4)_3+3C_2H_4O_2+3CO_2+11H_2O.$$

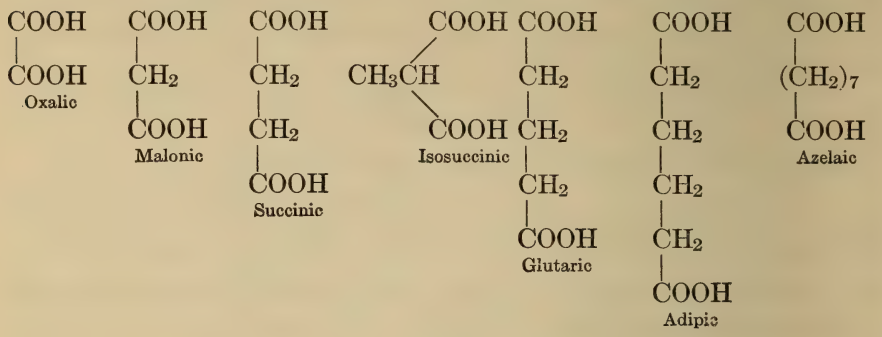
An accurately weighed quantity of the material (about .4 gram), or an aliquot part of the solution after having been made up to a definite volume, is, after suitable dilution, boiled gently for one hour with 10 mils of 10 per cent sulphuric acid and 25 mils of N/2 potassium bichromate in an Erlenmeyer flask, fitted with a reflux condenser. The excess of potassium bichromate is titrated in the usual manner with N/10 sodium thiosulphate after the addition of 10 mils of 10 per cent potassium iodide and 1 drop of starch paste. One mil N/2 potassium bichromate corresponds to .01127 gram of lactic acid.

If volatile matters which reduce chromic acid are present, they must be first removed by repeated evaporation. The presence of sugar, dextrin and similar materials renders this method useless, as they reduce chromic acid, and, moreover, cannot be separated. Good results are obtained with mixtures of double salts such as antimony calcium lactate and antimony sodium lactate, containing more or less great excess of free lactic acid. In this case, the antimony is first precipitated as sulphide by means of sulphuretted hydrogen, excess of the latter being subsequently expelled by boiling.

Lactic anhydride is not oxidized by the above treatment, and if present must be first converted into lactic acid by heating with a slight excess of alkali.

DICARBOXYLIC ACIDS

The relationship of the acids of this class is shown by the following:



Oxalic acid is not of importance therapeutically, but its salts occur in certain plants, and its identity may be important in establishing the presence of a certain drug. Succinic acid and the succinates are used in medicine. The other acids are of interest to us only from their chemical relation to the group as a whole.

Oxalic Acid

Oxalic acid forms colorless crystals containing two molecules of water, readily soluble in alcohol and water, and sparingly in ether. It melts at 100°, losing its water, and at 150° sublimes. When heated to a higher temperature it is decomposed into formic acid and carbon dioxide, or to carbon monoxide, dioxide, and water. When heated moderately with concentrated sulphuric acid it is decomposed and gives the final products as above. It has reducing properties, precipitating gold, and is readily oxidized by permanganate.

It is dibasic and forms salts with two equivalents of the metallic hydroxide, or with two molecules of a monohydric alcohol. It has fairly strong acid properties, decomposing carbonates and dissolving certain metallic oxides. The alkali oxalates are soluble in water, the acid alkaline salts and silver salts less so, and most of the other salts are insoluble or only sparingly.

Succinic Acid

Succinic acid crystallizes in colorless prisms, melting 180–182° and subliming readily. It is sparingly soluble in water, alcohol, and ether, and insoluble in chloroform and benzol. When strongly heated it forms the anhydride and the vapors produce coughing. It is very stable and little affected by oxidizing agents. It often sublimes without charring when strongly heated. When a soluble succinate is treated with ferric chloride, a rich brown precipitate is produced which might at first be mistaken for the precipitate given by benzoic acid. A solution is not precipitated by calcium or barium chlorides.

Sodium succinate is used as a saline cathartic, and also in combating infections of the gall bladder and biliary tract.

Succinic anhydride, $\begin{matrix} CH_2CO \\ | \\ CH_2CO \end{matrix}\!\!>\!O$, is prepared by heating the acid with phosphorus oxychloride for some time and then distilling. It is a colorless crystalline substance, melting 120°, and when boiled with water or an alkali is reconverted to the acid or a succinate. It is used in the preparation of succinic peroxide, the chemistry of which has been described unde Peroxides.

Succinic acid can be determined by shaking out with ether from a solution acidulated with mineral acid, and weighing the residue left on evaporation.

Ammonium succinate is used as a diuretic and an antispasmodic in cramps, hysteria, and delirium tremens.

Isosuccinic acid melts 130°, and sublimes readily. It does not form an anhydride and when heated alone, or with water, it is decomposed into propionic acid and carbon dioxide.

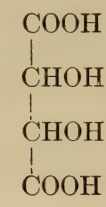
Identification of Succinic Acid—Treat .1 gram acid with .5 gram paratoluidin in a test-tube fitted with a cork stopper and an air cooler and heat for one-half hour in an oil-bath at 200–220°. Cool partially and add 10 mils dilute alcohol (1–1) and boil. Cool well and filter the succintoluide. Wash with 2 mils alcohol (1–1), crystallize from 5 mils boiling strong alcohol, filter, wash with 1 mil strong alcohol, dry at 100° and determine the melting-point, which should be 254.5–255.5° C.

Asparaginic, aspartic, or aminosuccinic acid, $COOHCH_2CH(NH_2)$-$COOH$, results when asparagin is boiled with acids or alkalies. It is sparingly soluble in cold water and alcohol, is readily soluble in hot water and alkalies. Asparagin occurs in many plants, but it has practically no use medicinally.

HYDROXYDICARBOXYLIC ACIDS

In this group we find malic and tartaric acids, the former of special interest to the food chemist, and the latter to the drug chemist.

TARTARIC ACID



Tartaric acid is extensively used in medicine. It is a refrigerant and an antiscorbutic, and in combination with alkalies is a mild laxative and diuretic. It enters into the combination of artificial effervescent mineral water salts and will sometimes be found in granular effervescent preparations together with citr c acid.

Seidlitz mixture consists of sodium and potassium tartrate (Rochelle Salt), sodium bicarbonate, and tartaric acid. Effervescent salts of the Carlsbad type contain sodium bicarbonate, tartaric acid, and sugar; of the Kissingen type, potassium and sodium chloride, magnesium sulphate, bicarbonate, acid, and sugar; of the Vichy type, sodium chloride, magnesium sulphate, potassium carbonate, sodium bicarbonate, acid, and sugar. As the bitartrate of potassium it will be found in combination with sulphur, and sometimes with camphor, opium, and Asclepias tuberosa; and with ipecac, arsenous acid, sodium benzoate, and Capsicum.

Tartaric acid should be 'ooked for whenever antimony is found, as it forms with this latter an important double salt known as Tartar Emetic. The various combinations containing this substance are described more fully under Antimony.

Tartaric acid exists in several forms, and their study from the point of view of stereoisomerism has been exhaustively considered and detailed at length in works on theoretical organic chemistry. These forms include the dextro, lævo, racemic or uvic, and meso. The racemic and meso are inactive, and the racemic can be resolved in both dextro and lævo by appropriate means, but the meso cannot. The dextro is the acid of common occurrence and is the form in which we are interested from an analytical standpoint.

The pure acid forms anhydrous, colorless, transparent rhombic prisms, melting 168–170° C. but not sharply as decomposition takes place. Specific gravity 1.74–1.75. It is readily soluble in water and alcohol, very slightly

in ether, and almost insoluble in chloroform and benzol. It chars with sulphuric acid or when slowly ignited, emitting the odor of burnt sugar. When heated some time at 150° it gives the anhydride and other compounds.

Neutral potassium salts give a crystalline precipitate with free tartaric acid, insoluble in acetic acid, but dissolving in mineral acids and alkalies. This precipitation is prevented if boric acid is in solution, which must be borne in mind when tablets are being tested, as boric acid is often present in tablets as a lubricant.

A solution of the free acid nearly neutralized with ammonia should give no precipitate with calcium sulphate. Oxalic and racemic acids will give a precipitate with this test.

When warmed in the presence of ammoniacal silver oxide, a silver mirror is deposited on the walls of the containing vessel.

Cinchonidin sulphate gives a white crystalline precipitate with free tartaric acid or its ammonium salt.

When a neutralized solution of tartaric acid is treated with a calcium salt, a precipitate is thrown down which is soluble in potassium hydroxide but which comes down again on boiling. The precipitate is also soluble in ammonium chloride. Calcium racemate is insoluble in acetic acid and nearly so in ammonium chloride.

Tartaric acid is broken up into the acetate and oxalate on fusion with potash. Nitric acid oxidizes it to oxalic acid. Tartaric acid in solution prevents the precipitation of iron and aluminum by alkalies.

Tartaric acid reduces alkaline permanganates.

The important salts of tartaric acid are the following:

Sodium and potassium tartrate. Rochelle salt or Seignettes salt.

Potassium antimonyl tartrate. Tartar emetic.

Potassium hydrogen tartrate. Cream of Tartar.

Salt of tartar is a misleading name applied to potassium carbonate.

When barium chloride is added to a solution of tartar emetic a precipitate is formed according to the equation.

$$2KSbOC_4H_4O_6 + BaCl_2 = Ba(SbOC_4H_4O_6)_2 + 2KCl.$$

The barium salt on decomposition with sulphuric acid gives an acid solution which soon deposits antimonous hydroxide, but if it is neutralized with potassium hydroxide before decomposition occurs it yields tartar emetic. It would indicate that the emetic was the potassium salt of a tartaric antimony acid, which has been called tartryl antimonous acid, and hences the emetic would be potassium tartryl antimonite.

When Sb_2O_3 is dissolved in tartaric acid, antimonyl tartrate $(SbO)_2$-$C_4H_4O_6$ is produced, and crystallizes from the solution on adding alcohol.

When this is boiled with normal potassium tartrate it is converted to tartar emetic, $(SbO)_2C_4H_4O_6 + K_2C_4H_4O_6 = 2KSbOC_4H_4O_6$.

Anilin antimony tartrate, $C_4H_5O_6SbOC_6H_7N$, is soluble in water, sparingly in alcohol, gives a violet color with calcium chloride, a white precipitate with hydrochloric acid, soluble in excess and a white precipitate with nitric acid soluble in large excess.

Cobalt nitrate solution gives a red color when added to an alkali tartrate, the coloring being discharged on adding excess of sodium hydroxide. If the alkaline solution is boiled a deep-blue color appears on again heating. Alkali citrates give an immediate deep-blue color in the cold with cobalt nitrate in the presence of alkali.

Tartar emetic does not behave like other tartrates with cobalt nitrate, the reaction being similar to that obtained with citrates.

A solution containing free tartaric acid yields a crystalline precipitate in the cold with 10 per cent solution of calcium formate, having a characteristic microscopic appearance. Citric acid gives no reaction in the cold, but on warming, a crystalline precipitate is obtained.

Detection of Tartaric Acid in Mixtures.—An aqueous solution of the product is precipitated with excess of lead acetate and the precipitate filtered, washed with water, and 50 per cent alcohol until free from lead, and the precipitate decomposed by hydrogen sulphide in the presence of a little ammonia. The solution is filtered from the lead sulphide and boiled to expel the excess of ammonia, and any ammonia sulphide formed, filtered again if any sulphur is precipitated, and portions tested as follows:

Ammoniacal silver oxide will give a silver mirror on warming; calcium chloride gives a precipitate in the cold, becoming granular on boiling and soluble in acetic acid; cinchonidin sulphate gives a precipitate of white needles not always appearing at first but gradually appearing as the solution stands.

The accompanying table shows the comparative reactions of the free hydroxy acids and their salts.

Determination of Tartaric Acid.—Tartaric acid when it occurs by itself can be estimated without difficulty, and when it occurs simultaneously with citric acid the potassium method will give good results. The accurate determinations of citric acid in presence of tartaric acid is still a matter for study.

Tartaric acid in an aqueous solution can be titrated directly with alkali using phenolphthalein as an indicator.

Tartaric in mixed preparations can be determined with fair accuracy by the method recommended for the determination of the total acid in wines. The method of the Association of Official Agricultural Chemists [1] is quoted herewith:

[1] Jour. A. O. A. C., Vol. 1, p. 240.

	KCl.	$CaCl_2$.			Ammoniacal Ag_2O.	Lead Acetate.		Calcium Hydroxide.		Fehling Solution.	Cinchonin.	Cinchonidin.	Quinidin.
		Cold.	Hot.	Add Acetic Acid.		Cold.	Hot.	Cold.	Hot.				
Citric Acid...	0	0	0	—	White ppt.	White ppt.	Coag.	No ppt.	Ppt. with excess	Reduction	No ppt.	No ppt.	No ppt.
Am. Cit.....	0	0	White ppt.	Insol.	Ppt. sol. on heating	White ppt.	Coag.	No ppt.	Ppt. with excess	No reduction	No ppt.	No ppt.	No ppt.
Sod. Cit.....	0	0	White ppt.	Insol.	No ppt.	White ppt.	Coag.	No ppt.	Ppt. with excess	Reduction	No ppt.	No ppt.	No ppt.
Tartaric Acid	Crystals	0	0	—	Mirror with excess sol.	White ppt.	Coag.	White ppt. with excess	Unchangedon heating	Reduction	No ppt.	White needles	No ppt.
Am. Tart....	Few crystals	White ppt.	Becomes granular	Sol.	Mirror	White ppt.	Coag.	White ppt. with excess	Unchanged on heating	Reduction	No ppt.	White needles	No ppt.
Sod. Tart....	0	White ppt.	Becomes granular	Sol.	Mirror	White ppt.	Coag.	White ppt. with excess	Unchanged on heating	Reduction	No ppt.	No ppt.	No ppt.
Lactic Acid..	0	0	0	—	Slight reduction	No ppt.	No ppt.	No ppt.	No ppt.	Reduction	No ppt.	No ppt.	No ppt.
Am. Lactate	0	0	0	—	Slight reduction	No ppt.	No ppt.	No ppt.	No ppt.	Reduction	No ppt.	No ppt.	No ppt.
Sod. Lactate.	0	0	0	—	No reduction	No ppt.	No ppt.	No ppt.	No ppt.	Reduction	No ppt.	No ppt.	No ppt.
Succinic Acid	0	0	0	—	White ppt.	White ppt.	White ppt.	No ppt.	No ppt.	Reduction	No. ppt.	No ppt.	No ppt.
Am. Suc.....	0	0	White crystals	Sol.	White ppt.	White ppt.	White ppt.	No ppt.	No ppt.	Reduction	No ppt.	No ppt.	No ppt.
Sod. Suc.....	0	0	White crystals	Sol.	White ppt.	White ppt.	White ppt.	No ppt.	No ppt.	Reduction	No ppt.	No ppt.	No ppt.
Malic Acid...	0	0	0	—	White ppt.	White ppt.	White ppt.				No ppt.	No ppt.	No ppt.
Am. Mal....	0	White ppt.	White ppt.		White ppt.	White ppt.	White ppt.				No ppt.	No ppt.	No ppt.
Sod. Mal....	0	White ppt.	White ppt.		Wihte ppt.	White ppt.	White ppt.				No ppt.	No ppt.	No ppt.

Neutralize 100 mils of the wine with N/1 sodium hydroxide, calculating from the ac dity, as determined by titration, the number of mils of N/1 alkali necessary for the neutralization. If the volume of the solution is increased more than 10 per cent by the addition of the alkali, evaporate to approximately 100 mils. Add to the neutralized solution .075 gram of tartaric acid for each mil of N/1 alkali added and, after the tartaric acid has dissolved, add 2 mils of glacial acetic acid and 15 grams of potassium chloride. After the potassium chloride has dissolved, add 15 mils of 95 per cent alcohol by volume, stir vigorously until the potassium bitartrate starts to precipitate, and then let it stand in an ice box for at least fifteen hours. Decant the liquid from the separated potassium bitartrate on a Gooch, prepared with a very thin film of asbestos, or on filter paper in a Buchner funnel. Wash the precipitate and filter three times with a few mils of mixture of 15 grams of potassium chloride, 20 mils of 95 per cent alcohol by volume and 100 mils of water, using not more than 20 mils of the wash solution in all. Transfer the asbestos or paper and precipitate to the beaker in which the precipitation was made, wash out the Gooch or Buchner funnel with hot water, using about 50 mils in all, heat to boiling and titrate the hot solution with N/10 sodium hydroxide, using phenolphthalein as an indicator. Increase the number of mils of N/10 alkali required by 1.5 mils to allow for the solubility of the precipitate. One mil of N/10 alkali is equivalent, under these conditions, to .015 gram of tartaric acid. Subtract the amount of tartaric acid added from this result to obtain the grams of total tartaric acid per 100 mils of wine.

Method Using Calcium Chloride.—Dissolve 5 grams of the tartrate-containing body in hydrochloric acid, filter if necessary. Neutralize with sodium hydroxide free from carbonate, add an excess calcium chloride, and after allowing to stand for some time collect the precipitate on a filter. Wash, dry, ignite, titrate with N/1 hydrochloric acid. Every 100 mils of N/1 acid required to neutralize CaO or $CaCO_3$ resulting from the ignition represents 7.5024 grams $H_2C_4H_4O_6$.

Kling and Florentine [1] have proposed a method for determining tartaric acid which they claim is of special application when working with products containing iron, aluminum, and antimony. Ammonium citrate is employed to replace the tartaric in its combinations with the metals mentioned. The following solutions are required: (*a*) Ammonium citrate 5 per cent; (*b*) ammonium *l*-tartrate free from *d*-tartrate, 2 per cent, preserved with 5 mils formaldehyde; (*c*) calcium acetate prepared by dissolving 16 grams calcium carbonate in 120 mils acetic acid and making up to 1 liter; (*d*) hydrochloric acid containing 40 grams at 22° B., per liter; (*e*) 5 grams calcium carbonate dissolved in 20 grams acetic acid

[1] Orig. Com. 8th Intern. Congr. Appl. Chem., 1, 237; Bul. Soc. Chem., 11, 886.

with 100 grams of sodium acetate per liter; (*f*) potassium permanganate, 1.6 per cent, standardized against a known solution of tartaric acid.

The tartaric acid is estimated by dissolving the sample in 150 mils water and treating the solution with 10–15 mils of solution (*a*), then 25 mils of solution (*b*), and 20 mils of solution (*c*), mixing and allowing to stand for twelve hours. It is then filtered, washed with cold water, and the precipitate transferred into another container, using 20 mils of solution (*d*) which dissolves the racemate, made up to 150 mils; 40–50 mils of solution (*e*) added and heated to 80° C. on a water-bath. When the solution has cooled and the precipitate settled, it is filtered, washed, dissolved in 10 per cent sulphuric acid, and titrated with permanganate. The factor obtained for tartaric acid in the racemate is divided by two and the amount of *d*-tartaric in the original solution determined.

Analysis of Granular Effervescent Salt.—Make a thorough admixture of sample, separate about 15 grams powder in a mortar and transfer to a weighing bottle.

(1) Weigh out exactly about 1 gram and determine the total CO_2 in absorption apparatus. Calculate to sodium and potassium bicarbonates.

(2) Determine phosphoric acid in .5 gram and calculate to sodium phosphate, $Na_2HPO_42H_2O$.

(3) Determine chlorine in 1 gram and calculate to sodium chloride.

(4) If magnesium is present determine in 1 gram and calculate to magnesium sulphate, $MgSO_47H_2O$.

(5) Determine sulphate in 1 gram and calculate to $MgSO_47H_2O$, and if any excess calculate to $Na_2SO_410H_2O$.

(6) Dissolve 1 gram in water, boil, and titrate. If acid, calculate to mixed citric and tartaric acids. This figure will give the acid in excess of that necessary to neutralize the bicarbonates. To determine the amount used up by the bicarbonates, figure back from the results obtained in No. 1. This amount plus the amount found in excess will give the total acids. The final figure is of course only approximate, but it will often come out within 1 to 2 per cent of the quantity known to have been added. There is no method of determining the relative quantities of citric and tartaric acids in a mixture of the two.

If the sample is alkaline, the determination in No. 1 of the total bicarbonate minus the excess alkalinity (figured to bicarbonate) will give the amount of alkalinity consumed by the mixed acids and from which figure they may be calculated.

In the official granular salts the proportion of tartaric and citric acids is about 3 to 2.

(7) Determine caffein in a 1-gram sample.

(8) If hexamethylenetetramine is present, determine ammonia in a 5-gram sample and calculate to hexamethylenetetramine. Caution must

be observed, too, in keeping sample dry and to add undiluted concentrated sulphuric acid.

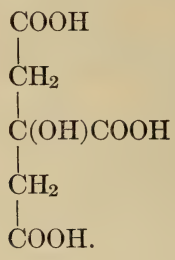
(9) Determine moisture in 1 gram by drying *in vacuo* over sulphuric acid.

(10) Make a qualitative test for lithium with spectroscope, and if advisable determine the quantity.

Many commercial tartaric acids and tartrates contain small quantities of lead, and their wholesomeness has become a problem for the food chemist. We are not especially concerned with the feature, but it may happen that the purity of a sample with respect to lead will be a question of importance in our work. The small quantity present is usually determined by color comparison, which is not a very safe method unless the absence of other heavy metals has previously been ascertained. Hence, in cases of moment or doubt the analyst ought to run careful qualitative tests before he attempts to arrive at any conclusions as to the quantity present.

HYDROXYTRICARBOXYLIC ACIDS

This group is represented by Citric Acid



Citric acid is used to considerable extent in medicine, occurring in a variety of products exploited for refrigerant and laxative purposes. It is somewhat antiseptic and antiscorbutic, is employed in pruritis, diphtheria, post partum hemorrhage, gangrene, sore mouth, excessive sweating, inflammation of the throat, and scurvy. Ammonium citrate is almost always present in preparations containing beef peptones, such as beef, iron and wine, and cod-liver oil wines.

It is present in granular effervescent salts and lithia tablets, and in combination with magnesium. It is a constituent of anti-fat mixtures combined with sugar.

Citric acid crystallizes with one molecule of water. When heated it dissolves in its water of crystallization and at 75° the water begins to evaporate. It becomes anhydrous at 135° and melts between that temperature and 152° C. Citric acid is efflorescent in warm air and deliquescent in moist air. Its presence in a sample is soon manifested if it is left exposed

in a laboratory. It dissolves in the water it attracts, and if sugar is present forms a sticky unsightly mass which is difficult to dry.

At a high temperature it gives aconitic acid, and on further heating itaconic and citraconic. When slowly ignited it is gradually decomposed without the odor of burnt sugar and it dissolves in hot sulphuric acid with a brownish-yellow color, instead of the charring phenomenon characteristic of tartaric acid.

It is readily soluble in alcohol and water, slightly in ether, and practically insoluble in chloroform, benzol, and petroleum ether.

It gives no precipitate with potassium chloride or acetate. Calcium hydroxide in excess gives a precipitate on boiling, which redissolves on cooling. When this test is performed, a little calcium may be precipitated by the carbon dioxide in the air, and when the solution is cooled the precipitate will not entirely dissolve. Calcium citrate is insoluble in potassium hydroxide, but soluble in ammonium chloride and acetic acid. Neutral citrates are precipitated by calcium chloride on boiling, but free citric acid gives no precipitate.

It does not reduce alkaline permanganate nor ammoniacal silver oxide.

Citric acid in solution prevents the precipitation by alkalies of iron and zinc.

It dissolves iron oxide, and on evaporating the liquid it will remain clear and finally scale when dry; tartaric acid dissolves the oxide, but on evaporating a precipitate occurs.

Fusion with potash gives acetate and oxalate. When heated with hydriodic acid it is converted to tricarballylic acid,

$$COOH \cdot CH = (CH_2COOH)_2.$$

Detection of Citric Acid.—Citric acid can be precipitated from its solution by lead acetate and the precipitate washed and decomposed by hydrogen sulphide exactly as described under the Detection of Tartaric Acid. The solution of ammonium citrate should then be tested with calcium chloride, calcium hydrate, and the other reagents noted in the table on page 651.

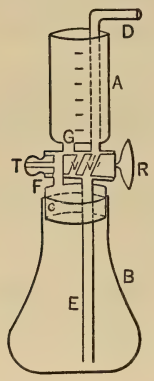
L. Gowing–Scopes [1] proposes the following method, which he states is accurate in the presence of tartaric, succinic, oxalic, benzoic, and phosphoric acids, but when malic, lactic, or salicylic acids are present the results are too high. The sample containing not over .04 gram of citric acid is exactly neutralized with N/10 alkali, using phenolphthalein, treated with 10 mils of a reagent (consisting of 68 mils conc. nitric acid, 51 grams mercuric nitrate, 51 grams manganese nitrate; 100 mils water, finally made up to 250 mils and filtered) diluted to 200 mils and heated three hours with a reflux. The precipitate is washed by decantation,

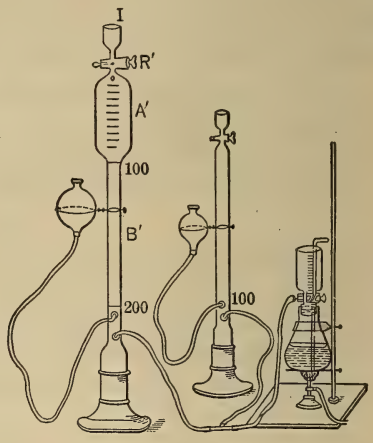
[1] Analyst, 1913, 38, 12.

collected in a tared Gooch, and dried at 100° for five hours, one-sixth of the weight of the precipitate gives the amount of citric acid. The residue should be cream colored, any yellowish coloration indicating the formation of basic salts, which will cause too high results.

Citric Acid in citrates and lemon juice [1]

The method consists in decomposing the citric acid (first separated as calcium citrate) by gently warming with concentrated sulphuric acid and measuring the evolved carbon monoxide, 1 molecule of which is obtained from each molecule of citric acid. The apparatus used is shown in the accompanying figures. The upper part *A* is fitted to the flask *B*





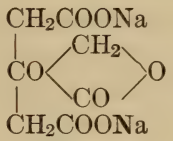
(150-mil capacity) by a ground joint, and the tubes *D* and *E* and *G* and *E* may be connected respectively through the tap *R*, as also may the flask and the exterior. Two grams of the calcium citrate, moistened with water, are introduced into *B*, and the air in the flask is completely displaced by carbon dioxide, the absence of air being ascertained by means of an auxiliary nitrometer, filled with potassium hydroxide solution (1 : 5) and attached to the T-piece; 25 mils of concentrated sulphuric acid are then run into *B* from *A*, and a slow current of carbon dioxide is again passed into the flask, which is warmed to 80–100° C. and occasionally shaken, the carbon monoxide evolved being collected in a nitrometer of 200 mils capacity, of which the lower part B^1 (100 mils capacity) is graduated in fifths of a mil. When the volume of gas becomes constant, the nitrometer is allowed to stand for half an hour and then, after washing the gas with potassium hydroxide solution, introduced through *I*, the volume is read, and the usual corrections are made for temperature and press-

[1] M. Spica., Chem. Zeit., 1910; 34, 1141.

ure. One mil of carbon monoxide, at 0° C. and 760 mm. indicates .009407 gram of citric acid ($C_6H_6O_7$, H_2O). The same apparatus may be used for the determination of carbonate in a citrate, by decomposing with a known volume of concentrated hydrochloric acid and measuring the evolved carbon dioxide over water.

Citarin

Sodium anhydromethylene citrate is the normal sodium salt of anhydromethylene-citric acid.

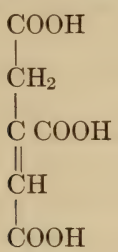


Citarin

Anhydromethylene-citric acid is obtained by reacting on citric acid with paraformaldehyde, or with chlormethyl alcohol, CH_2ClOH.

It is a white, granular, somewhat hygroscopic powder, having a faintly saline and aciduous taste, and a slightly acid reaction. It is readily soluble in about 1.5 parts of water, but insoluble in alcohol. Its solution splits off formaldehyde when heated, particularly in the presence of alkalies, and mineral acids separate from its concentrated solutions methylene-citric acid. It is incompatible with acid and alkalies and is decomposed by heat. It is claimed to be useful for gout and chronic rheumatism.

Aconitic Acid



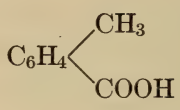
This acid is produced on heating citric acid to a high temperature. It occurs naturally in aconite tubers, larkspur, black hellebore, yarrow, Equisetum, and probably other plants.

CHAPTER XVIII

ORGANIC ACIDS—AROMATIC SERIES

CARBOXYLIC ACIDS

The aromatic carboxylic acids may be considered as derived from the hydrocarbons of that series by the substitution of one or more carboxyl groups for a corresponding number of hydrogen atoms. Two classes of compounds may be obtained, depending on whether the substitution is in the nucleus or in the side chain. Thus we may have toluic acid,



or phenylacetic acid, $C_6H_5CH_2COOH$, both from toluene.

These acids may be obtained by oxidizing alcohols or aldehydes, by the hydrolysis of nitriles by alkalies or mineral acids, or by oxidizing the homologues of benzene with dilute nitric or chromic acid. In the latter case only acids which contain the carboxyl group united to the nucleus can be obtained, because the side chain is always oxidized to carboxyl, no matter how many CH_2 groups are present.

The aromatic acids are crystalline and may be distilled with steam without change. They are soluble in ether and alcohol and some of them fairly readily in petroleum ether, sparingly in cold water, but to a much greater degree in warm water. In all reactions affecting the carboxyl group they are analogous to the aliphatic acids, and give corresponding derivatives. Benzoic acid gives sodium benzoate, C_6H_5COONa, ethyl benzoate, $C_6H_5COOC_2H_5$, benzoyl chloride, C_6H_5COCl, benzamide, $C_6H_5COONH_2$, benzoic anhydride, $(C_6H_5CO)_2O$.

When distilled with calcium oxide they are decomposed with the formation of the corresponding hydrocarbons.

Two of the acids of this group, benzoic and cinnamic, are very important in medicinal chemistry. They occur both in the free state and in combination in the aromatic balsams of Peru and Tolu, and their salts are employed to a considerable extent. These two acids with salicylic and its many derivatives, gallic and tannic acids, which are members of the

hydroxycarboxylic group, and phenolsulphonic acid and its derivatives, are the principal acids of the aromatic series of medicinal importance.

BENZOIC ACID, C_6H_5COOH

Benzoic acid is obtained from several sources, benzoin, toluol, naphthalene, and urine. It is, of course, the same individual no matter what its source, though practitioners often ascribe different properties, depending on its origin. If a difference actually occurs it is probably due to the effect or absence of impurities in an article of ordinary commercial purity.

Benzoic acid is a stimulant expectorant, and is an ingredient of bronchitis mixtures. It is used for uric acid gravel, cystitis, acute gonorrhorea, and nocturnal incontinence. Its antiseptic value is well known and it takes part in the formulas of many mouth washes and douches for the nose and throat. Sodium benzoate is used in gout and rheumatism. Lithium benzoate often occurs in lithia tablets.

Benzoic acid is used in surgeon's gauze. It is one of the ingredients of liquid camphor compound with opium, camphor, and oil of anise. In Brown's mixture it occurs with licorice, oil anise, powdered opium, camphor, and tartar emetic, with and without ammonium chloride. Cystitis tablets are composed of benzoic acid, borax, buchu, triticum, corn silk, Hydrangea and atropin sulphate. Mentholated throat tablets contain benzoic acid, menthol, anise, cocain, and eucalyptol.

Sodium benzoate is an ingredient of nasal tablets and liquid nasal douches with bicarbonate, chloride, biborate, salicylate of sodium, thymol, menthol, oils of eucalyptus and gaultheria. It also occurs in tooth pastes. It is combined with caffein in hypodermic tablets.

The acid prepared from benzoin usually carries the suggestion of the characteristic odor of the drug and may be slightly darker in color than the artificial acid. These characteristics, however, do not necessarily determine its origin, for it is possible to impart the same properties by subliming benzoic acid in presence of a little gum or by adding a small quantity of vanillin. Artificial benzoic acid may contain chlorinated products, traces of hydrochloric, sulphuric, or hippuric acid.

Benzoic acid occurs in iridescent needle-shaped crystals, or in fine needles, melting 120–121°, soluble in most organic solutions, in hot water and slightly in cold water. It sublimes at the temperature of the water-bath and by this may be readily purified, and crystals obtained which give a sharp melting-point. Its vapor has a characteristic odor and an irritating action on the throat, producing violent coughing.

Benzoic acid gives a flesh-colored precipitate with ferric chloride, and the reaction is best obtained by dissolving the acid in a little dilute ammonia and evaporating off the excess of gas. On dissolving the residue in water and adding the reagent a copious precipitate is thrown down.

It gives no precipitate with bromine water, which distinguishes it sharply from salicylic acid. This property furnishes a ready and simple method of separating the two acids when they occur together.

It does not give the odor of benzaldehyde when warmed with permanganate, being distinguished in this respect from cinnamic acid. The latter acid is furthermore unsublimable at the temperature of the water-bath under ordinary conditions.

Benzoic acid yields benzene when distilled with excess of lime. When its vapors are passed over heated zinc dust benzaldehyde is formed. On distilling with phosphorus pentachloride, benzoyl chloride, C_6H_5COCl, is formed. The anhydride results when benzoyl chloride is treated with sodium benzoate. Both the anhydride and benzoyl chloride react with bodies containing an hydroxyl group giving benzoyl derivatives.

Ethereal salts of benzoic acid are obtained by dissolving the acid in the appropriate alcohol, saturating with hydrochloride acid gas, and after standing for some time, pouring the mixture into water when the ethereal salt separates. Ethyl benzoate has a pleasant aromatic odor, and its formation under appropriate conditions furnishes one of the conclusive tests for cocain.

Benzamide, $C_6H_5COONH_2$, may be obtained by treating ethyl benzoate with ammonia.

Benzonitrile, C_6H_5CN, is obtained by dehydrating benzamide or by treating diazo-benzene chloride with potassium cyanide and copper sulphate according to Sandmeyer's reaction.

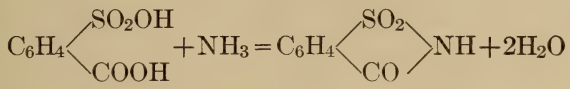
$$C_6H_5N_2Cl+KCN=C_6H_5CN+KCl+N_2$$

Meta-brom benzoic acid, melting 155°, is obtained when benzoic acid is heated with bromin and water to 125°. The ortho and para acids, melting 148 and 237° respectively, are obtained by oxidizing the corresponding bromtoluenes with nitric acid. The nitro benzoic acids are produced in a similar manner. The nitro acids on reduction with nascent hydrogen yield the corresponding amido benzoic acids, $C_6H_5(NH_2)COOH$, which form salts with both acids and alkalies.

The amido acids are of special interest, as they are the parent substances of a class of esters used as anesthetics. Propaesin and anesthesin are the propyl ester and ethyl ester of the para acid. The ortho acid melts 144–145°, the para 186–187° and the meta 173–174° C.

Beta-naphthol benzoate, benzoyl salicylic methyl ester, guaiacol benzoate, eugenol benzoate, hydrocotoin, will be described at length under Ethereal Salts. Benzoylphenylhydrazine and benzoylanilide will be mentioned under Nitrogen Compounds and Amines. Benzoyl acetyl peroxide is described under Peroxides.

Benzoic acid is converted into meta-sulphobenzoic acid when heated with sulphuric acid, and small quantities of para are produced at the same time. The ortho acid is obtained by oxidizing toluene orthosulphonic acid, it gives an imide known as saccharin when heated with ammonia.



The sulpho acids yield hydroxy acids when fused with potash.

Mohler's [1] test for benzoic acid, modified by von der Heide,[2] has been used extensively at the Bureau of Chemistry in testing food products. The suspected residue is dissolved in 1–3 mils of N/3 sodium hydroxide and evaporated until all the water is driven off. To the residue 5 to 10 drops of concentrated sulphuric acid and a small crystal of potassium nitrate are added, and the mixture heated ten minutes in a glycerol bath at 120–130°, or for twenty minutes in a boiling water-bath.

Meta-di-nitro benzoic acid is formed and the mixture is cooled, 1 mil water added and an excess of ammonia and boiled to break up any ammonium nitrite which may have been formed. After cooling, the solution, which should be in a test-tube, is treated with a drop of freshly prepared colorless ammonium sulphide without allowing the layers to mix, and the appearance of a red-brown ring indicates benzoic acid; on mixing, the color diffuses through the whole liquid, and on heating changes to greenish yellow, owing to the decomposition of the amido acid. Both cinnamic and salicylic acids yield amido acids, which give a red-brown ring, but the color is not destroyed on subsequent boiling. Phenolphthalein interferes with the test.

Jonescu [3] recommends a simple test in which the suspected residue is dissolved in water slightly acidified with acetic acid, and ferric chloride and a few drops of hydrogen peroxide added. The liquid assumes a yellow tint, which gradually becomes violet owing to the conversion of benzoic acid to salicylic.

Modified Jonescu Reaction.—One to 5 mg. of the acid in aqueous solution are treated with 3 drops of ferric chloride (26 per cent (anhydrous basis) diluted 1–10), 3 drops hydrogen peroxide 1–10, and 3 drops ferrous sulphate 3 per cent, shaking after each addition. In about thirty seconds the reaction commences and the violet coloration attains its maximum in five to ten minutes.

In the general scheme of analysis of medicinal preparations, benzoic

[1] Bul. Soc. Chim., 1890, 3 (3), 414.
[2] Zts. Nahr. Genussm., 1910, 19 (3), 137.
[3] J. Pharm. Chem., 1099 (4), 29, 523.

acid will appear on shaking out the acid solution with petroleum ether. If none comes out at this point, but on shaking out subsequently with ether an impure residue is obtained which on testing apparently contains benzoic acid, it is evident that a small quantity only is present in the product. The residue left on evaporating petroleum ether is always purer than that obtained with ether, for this latter solvent has a solvent action on a wider range of substances.

The crystalline residue should be examined first by allowing it to remain on top of the water-bath, but not over the direct steam, and observing any sublimate which may collect on a watch-glass placed over the top of the receptacle. Benzoic acid soon collects in beautiful iridescent stalactites which can be easily scraped off and their melting-point determined. The sublimate should also be subjected to Mohler's reaction and another portion dissolved in dilute ammonia, evaporated, and a solution of the residue treated with a drop of ferric chloride.

Salicylic acid sublimes more slowly than benzoic and collects in quantity on the sides of the flask. Acetanilid also sublimes and might be mistaken for benzoic acid, but it is readily detected by the carbylamine reaction. Cinnamic acid does not sublime under these conditions. If salicylic acid or acetanilid occur simultaneously with benzoic acid, they should be separated before making the chemical test. The residue may be dissolved in water with a little acetic acid and precipitated with bromin water. On filtering, the benzoic acid will be in the filtrate, and after destroying the excess of bromin it can be shaken out and tested.

Before attempting to determine the quantity of benzoic acid in a drug product, it is absolutely necessary to identify the other ingredients, and if other acids are present, their influence on the method must be taken into consideration, and appropriate procedures for their elimination conducted.

If the sample is a tablet it should be thoroughly extracted with alcohol and the solvent evaporated in the presence of a slight excess of alkali. If the sample is a liquid the alcohol should be evaporated under similar conditions. The residue is then diluted with water, transferred to a separator and slight excess of hydrochloric acid added. It is then shaken with four successive portions of chloroform, using 70, 50, 40, and 30 mils, the combined solvents washed with water or saturated sodium chloride, the chloroform partly recovered by distillation and the balance evaporated to dryness in a beaker at room temperature, using a blast of dry air to hasten the evaporation. The residue of benzoic acid is dissolved in neutral alcohol, about one-fourth the volume of water added, and titrated with N/10 sodium hydroxide, using phenolphthalein as indicator. One mil N/10 alkali = .01217 benzoic acid.

Salicylic acid if present can be separated and determined at the same

time by dissolving the chloroform residue in warm water acidulating with acetic acid, cooling, and precipitating the salicylic acid with excess of bromin water, filtering and weighing the tribromphenol bromide as described under salicylic acid, and then shaking out the benzoic acid from the filtrate exactly as described above.

If phenolic substances are present the residue must be dissolved in chloroform and shaken out three times with 10 per cent sodium bicarbonate, which will remove the acids, and the alkaline solution acidified and again shaken out with chloroform.

Cinnamic acid can be determined in presence of benzoic by treating a solution faintly acid with sulphuric acid with excess of standard bromin in potassium bromin, and after allowing the mixture to stand tightly corked, agitating occasionally, potassium iodide is added and the liberated iodin titrated with thiosulphate. The dilution of the cinnamic acid should be about 1–200. This method permits the simultaneous determination of both acids. The titration or gravimetric figure for the two is obtained, and then the solution in alkali is acidulated and the cinnamic acid determined. Garsed [1] described this method in his work on the Assay of Crude Cocain.

There are a number of proprietary products containing small amounts of aromatic balsams the presence of which can be ascertained by detecting the acids. If the sample is evaporated until all the water is driven off and then extracted with alcohol, the balsams will dissolve, and on concentrating and adding a little potash and boiling, the ester will be saponified and on evaporating the alcohol, dissolving in water, acidifying with hydrochloric acid and shaking with ether or chloroform, the benzoic or cinnamic acid or both will go into solution, and on carefully evaporating the solvent they will be left in the residue and can be identified.

HIPPURIC ACID. BENZOYL AMINO ACETIC ACID, $C_6H_5CONHCH_2COOH$

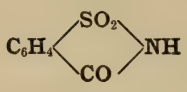
Hippuric acid occurs in the urine of herbivorous animals, from which it may be obtained in crystals, melting 187.5°. It decomposes at a higher temperature, giving a sublimate of benzoic acid and an odor suggestive of hay, followed by one characteristic of hydrocyanic acid. It is difficultly soluble in ether and cold water, more readily in hot water, and easily in alcohol and ethyl acetate. Calcium hippurate is used in cystitis, lithiasis, difficult dentition, and uric-acid diathesis.

Methylene Hippuric Acid—Hippol

This substance, about which there seeems to be some ambiguity as to its formula, is used as an urinary antiseptic. It melts 151°, and is soluble in alcohol, chloroform, ethyl acetate, and slightly in water.

[1] Pharm. J., 1903, 784.

SACCHARIN



Saccharin is sold under a variety of names, including garantose, gluside, glycophenol, glycosine, saccharinol, saccharinose, saccharol, saxin, sykose, zucherin, glusimide, agucirina, toluolsuss, neo-saccharin, etc.

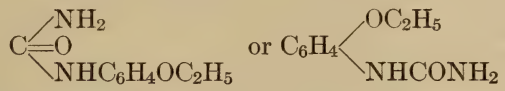
It is prescribed in cystitis and for sweetening foods and preparations used in diabetes and for obesity; to cover the bitter taste in certain products, and as a general sweetener in pharmaceuticals. It is usually sold in tablet form with or without sodium bicarbonate. It is a common sweetener used in tooth pastes.

It is a white or yellowish, odorless, microcrystalline powder, melting 220°, somewhat soluble in water, and completely soluble in alkaline solutions from which it is precipitated on the addition of mineral acid if the solution is concentrated. It dissolves readily in alcohol and ether, but is practically insoluble in petroleum ether, chloroform, and benzol.

It is best known on account of its intense sweet taste, which is apparent at considerable dilution. In order to compare its sweetening power with that of other substances, equal amounts should be dissolved in water containing, if necessary, sufficient bicarbonate to effect solution, and then each solution diluted until no sweet taste is apparent, the difference in dilution being a measure of the comparative sweetness.

As it appears in analysis, saccharin is usually an amorphous residue which is left on evaporating the ether shake-out from an acid solution. It will be indicated on removing a small quantity on the end of the finger and touching it to the end of the tongue. Its presence should be further substantiated by dissolving the residue in ether and shaking out with dilute sodium hydroxide, which will remove the saccharin, but will leave any dulcin or other sweetener in the ether. The alkaline solution is transferred to a test-tube, immersed in an oil-bath, the water evaporated and the temperature raised to 250° and held at that point for about twenty minutes. The alkaline mass is then dissolved in water, acidulated and shaken with ether, and the residue left on evaporation tested for salicylic acid, which results on fusing saccharin. The absence of salicylic acid in the original material must be assured by previously testing a portion with dilute ferric chloride. If salicylic acid is found, it can be separated by dissolving the residue in warm dilute hydrochloric acid, cooling, precipitating the acid with bromin water, filtering and boiling the filtrate to expel the excess of bromin, then adding a piece of sodium hydroxide and proceeding with the alkaline fusion as described above.

Dulcin is an entirely different chemical substance and may be considered either as a derivative of urea or phenetidin:



It is also used as an artificial sweetener, but is not as intense in its power as saccharin.

Licorice root contains a sweet substance, glycyrrhizinic acid, and Eupatorium rebaudianum also contains a sweet principle.

Saccharin can be readily determined when it occurs by itself or with bicarbonate, by dissolving the tablet in water, and precipitating with hydrochloric acid and shaking out with ether. On filtering and evaporating the ether the saccharin will be left as a weighable residue.

It can be separated from salicylic acid by means of bromin water, after the manner described for separating that substance from benzoic acid, and then shaken out with ether and weighed.

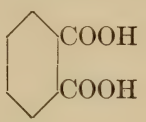
When it occurs in mixtures with other substances soluble in chloroform these may be dissolved out by the chloroform and the saccharin subsequently shaken out with ether. This method applies to products of the headache remedy type containing caffein, acetanilid, or acetphenetidin, all of which are removed from an acid solution by shaking out with chloroform.

Soluble saccharin is prepared by treating saccharin with sufficient aqueous ammonium carbonate to render it soluble and evaporating the solution to dryness.

PHTHALIC ACIDS

These are dibasic acids, and the ortho acid is the most important.

Ortho phthalic or benzene-*o*-dicarboxylic acid,



is a colorless crystalline substance, melting at 184° with formation of the anhydride, this being the only phthalic acid capable of forming an anhydride. If the melting-point of the new substance is taken it will be found to be 128°. The acid is soluble in water, alcohol, and ether, and forms well-defined metallic salts and esters.

When heated with resorcinol and a drop of sulphuric acid, fluorescein is produced, and the reddish-brown product when dissolved in dilute alkali and poured into water gives a yellowish-green fluorescent solution. This

reaction is given by all the ortho dicarboxylic acids of the benzene series, but not the meta and para acids.

Phthalyl chloride, boiling 275°, is obtained on heating the anhydride with phosphorus pentachloride.

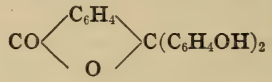
The anhydride sublimes readily in long needles, melting 128° and boiling 284°. It dissolves readily in alkalies, yielding salts of phthalic acid. On fusion with phenol in presence of zinc chloride it yields phenolphthalein.

Isophthalic acid is the meta form. It melts above 300° and when strongly heated sublimes unchanged. It is very sparingly soluble in water. Methyl isophthalate, $C_6H_4(COOCH_3)_2$, melts at 65°.

Terephthalic acid, the para form, sublimes without melting. The methyl ester melts 140°.

To prepare the methyl esters for identification the acid is warmed with phosphorus pentachloride and the clear solution poured into an excess of methyl alcohol. When the vigorous reaction has subsided, the liquid is poured into water, the separated salt collected, recrystallized, dried on a porous plate and then *in vacuo*.

PHENOLPHTHALEIN



This substance, which is a derivative of phthalophenone, is prepared by heating 3 parts of phthalic anhydride with 4 parts phenol and 5 parts powdered zinc chloride at 115–120° for eight hours. The product is washed with water, dissolved in sodium hydroxide, filtered, and phenolphthalein precipitated with acetic acid.

It has attained considerable importance in medicine as a laxative and will be found alone and in combination. It occurs as a white or faintly yellow crystalline powder, melting at 250°, readily soluble in alcohol, ether, and alkalies, and slightly soluble in water. The alkaline solutions are deep pink, the acid colorless. It is removed from an acid solution by shaking with ether and will be indicated by shaking out a portion of the ether solution with ammonia. Some of the anthraquinone derivatives occurring in rhubarb, senna, cascara, and other laxative drugs will give a pink color under similar conditions, but these derivatives are yellow and the yellow color is imparted to the ether, while the phenolphthalein is colorless in ether.

The anthraquinone derivatives dye wool a yellow color from an acid bath. The color is stripped by dilute ammonia and will give a second dyeing. An alcoholic solution of these derivatives on evaporation with

ferric chloride leaves a yellow residue; phenolphthalein under similar condition leaves a pinkish residue with odor of phenol, the color disappearing on cooling or in the presence of moisture. Phenolphthalein goes onto wool, but no color is imparted, if the treated wool is dropped into dilute ammonia the characteristic pink color will appear.

The separation of phenolphthalein from the anthraquinone derivatives has been described in the chapter on the Anthraquinone Drugs.

Several derivatives of phenolphthalein are used in medicine, among which are the dicinnamate, diisolverate, dibutyrate, salicylate, and carbonate. Halogen derivatives are obtained by heating phenols with halogenated phthalic acid in presence of dehydrating agents. The product obtained from phenol and tetrachlorphthalic and melts at 316°.

Tetraiodophenolphthalein or Nosophen

$$(C_6H_2I_2OH)_2\,C\begin{cases} C_6H_4 \\ O \end{cases}CO$$

This substance, also known as Iodophen, is a light-yellow, odorless, tasteless powder insoluble in water and acids, soluble in ether, chloroform, and alkaline solution, and melting with decomposition at about 225° C. It is used as an antiseptic, sometimes being substituted for iodoform.

The sodium salt is sold under the name Antinosin, and is a blue powder. It is used in a weak solution for spraying the mouth, nose, and throat in diphtheria, and for other affections of the mucous membrane.

The bismuth salt is called Eudoxin. It is a reddish-brown, tasteless powder, insoluble in water, used as an intestinal antiseptic.

IODONE

Iodone is prepared by treating a solution of phthalic-acid anhydride in acetic ether, with a solution of iodin and potassium iodide and crystallizing the product from suitable solvents.

It occurs in the form of dark green prismatic crystals which melt with decomposition at 163° C. When freshly prepared it is odorless, but on standing, traces of iodin are liberated, giving it a faint odor of iodin. It is gradually decomposed into phthalic acid, iodin, and potassium iodide by water, in which the decomposition products dissolve until a saturated iodin potassium iodide solution results. Any excess of iodin remaining in contact with the supernatant liquid remains unchanged. Alcohol, chloroform, and ether decompose iodone, but more slowly than water. Iodone crystals are stable in dry air; exposed to damp air, they gradually liberate iodin.

CINNAMIC ACID, $C_6H_5CH=CHCOOH$

Cinnamic acid is one of the best known unsaturated acids of the aromatic series and is of great importance in drug work. It occurs free and combined in the aromatic balsams of Peru and Tolu and in storax, and as an ester in the aloeresinotannol of Barbadoes aloes. It is prepared commercially from these sources, and also by heating benzaldehyde with acetic anhydride and anhydrous sodium acetate. This reaction is known as Perkin's reaction and is a general one for the preparation of unsaturated aromatic acids.

$$C_6H_5CHO+CH_3COOH=C_6H_5CH=CHCOOH+H_2O$$

Cinnamic acid is employed in the treatment of tuberculosis and lupus. It is used alone and in combination with arsenic and opium and with cocain. It will be found chiefly, however, in the aromatic balsams, which are used to a large extent, and its chemistry is, therefore, intimately connected with these drugs.

Cinnamic acid is unsaturated. It crystallizes from water in needles melting 133–135°, boils 300–304°, soluble in alcohol, ether, chloroform, and petroleum ether. It distills with steam, but does not sublime at the temperature of the water-bath. It combines directly with bromine, yielding phenyl $\alpha\beta$-dibrom propionic acid, $C_6H_5CHBrCHBrCOOH$. On reduction with sodium amalgam it is converted into phenylpropionic acid, melting 48–49°. When distilled with lime it is decomposed into carbon dioxide and phenyl ethylene or styrolene.

$$C_6H_5CH=CHCOOH=C_6H_5CH=CH_2+CO_2$$

Concentrated nitric acid converts it into a mixture of ortho and paranitrocinnamic acids. The para acid is readily separated from the ortho and identified by its melting-point.

Cinnamic acid when warmed with permanganate is converted in part to benzaldehyde, which is recognizable by its odor.

It may be further identified by the formation of the para nitro compound.

Stir .1 gram of the acid into 3 mils fuming nitric acid. It will dissolve at first, but a precipitate soon appears. Add 30 mils of cold water, stir, filter, and wash with 10 mils cold water. Transfer the precipitate to a test-tube and boil with 5 mils alcohol, cool, shake, filter and wash with 5 mils cold alcohol. Boil the precipitate with 5 mils ether, cool, shake, filter and wash with 5 mils cold ether, dry precipitate at 100° and determine the melting-point of the paranitrocinnamic acid, which softens

at 270° and melts at 286–287°. Any orthonitro acid or nitrobenzoic acid formed will be removed by the alcohol and ether.

It has been claimed that cinnamic acid prepared from Storax differs slightly from the synthetic acid in melting-point, and in the character of its crystalline form, but it is probable that any difference is due to small quantities of impurities.

Cinnamic acid can be titrated directly by alkali by dissolving it in neutral alcohol, using phenolphthalein.

When it is the only ether soluble acid present in a mixture, it can be determined by dissolving the sample in water, acidifying with dilute sulphuric acid and shaking out with ether. The ether is washed, filtered, and evaporated at a low temperature or spontaneously and the acid titrated as above.

In the case of products which do not dissolve in water, but which may be soluble in ether, the sample is treated with the solvent, filtered if necessary and the ether solution shaken several times with 10 per cent sodium bicarbonate. The alkaline liquid is then acidulated with sulphuric acid and the cinnamic acid shaken out with ether and determined.

When the cinnamic acid occurs in esters, resort must be had to saponification. Usually a certain amount of free acid is present at the same time and if desired, both the free and combined acid can be separately determined in one sample. The product is treated with ether and the solution filtered into a separator and shaken out with bicarbonate to remove the free acid which is determined as above described. The ether solution is then treated with excess of alcoholic potash and boiled under a reflux condenser. The alcohol is finally evaporated and the residue dissolved in water, filtered into a separator, the cinnamic acid set free from the potassium salt with sulphuric acid, shaken out with ether and finally titrated.

Sodium metaoxycyanocinnamate Zimpher

$C_6H_4(OH)CH=CCNCOONa$

This a yellowish-white crystalline substance soluble in water and dilute alcohol. It is used in dyspepsia and in gastro-intestinal atony.

TRUXILLIC ACID

Truxillic acid, which is a dicinnamic acid, has been described at length under the Coca Alkaloids.

Atropic Acid, $CH_2=C\cdot C_6H_5—COOH$.

Atropic acid is obtained on boiling tropic acid for a long time with barium hydroxide. It melts 106–107°, is volatile with steam and soluble in alcohol, ether and slightly in water.

Isatropic Acids, α and β.

These acids result on heating atropic acid. The α acid is

$$C_6H_5CCOOHCH_2C_6H_4CHCOOHCH_2.$$

It melts 237–238°. The β-acid melts 206°.

Tropic Acid, $C_6H_5CH(CH_2OH)COOH$.

Tropic acid is one of the hydrolytic products of atropin. It melts 117–118° and is soluble in alcohol, ether and hot water.

HYDROXY CARBOXYLIC ACIDS

There are two classes of these acids according as the OH group is in the nucleus or the side chain. In the first case they have phenolic characteristics, and such acids are both phenols and acids. In the second case they have alcoholic characteristics, and compounds of this class, such as mandelic acid, $C_6H_5CHOHCOOH$, have properties closely resembling those of the fatty hydroxy acids.

The first class contains two acids, which are of especial importance in drug work, salicylic and gallic. The hydroxy acids of this class may be prepared from the hydrocarbons by forming the nitro-compounds and then the amido compounds, which on treatment with nitrous acid gives the hydroxy acid. They also result when the aromatic acids are sulphonated and the sulphuric acids fused with potash, the meta compounds resulting by this method. The ortho acids result generally when a sodium phenolic compound is heated to about 200° C. in a stream of carbon dioxide. Most dihydric and trihydric phenols may be converted into the corresponding hydroxy acids by heating them with ammonium carbonate or potassium bicarbonate. Another method consists in boiling a strongly alkaline solution of a phenol with carbon tetrachloride, the ortho acid resulting in greatest amount with varying proportions of the para.

$$C_6H_5ONa+CCl_4+5NaOH=C_6H_4\begin{cases}COONa\\OH\end{cases}+4NaCl+3H_2O$$

These acids are colorless crystalline solids more readily soluble in water and less volatile than the acids from which they are derived, and soluble in the ordinary organic solvents. When heated with lime they are decomposed with the formation of phenols and carbon dioxide. The ortho acids give color reactions with ferric chloride, but the *m*- and *p*-acids give no coloration.

They form salts with carbonates and with the calculated quantity of caustic alkali, but when an excess of alkali is added the hydrogen of the OH group is displaced. The di-metallic salts are decomposed by

carbon dioxide with the formation of mono-metallic salts, but the metal in the carboxyl group cannot be displaced by it in this way. They yield well-defined precipitates with bromin.

The ethereal salts are prepared by saturating a solution of the acid in the proper alcohol with hydrogen chloride. By this treatment only the hydrogen of the carboxyl is displaced and normal salts such as methyl salicylate are produced. These compounds still have phenolic properties and dissolve in alkalies, forming metallic derivatives such as methyl potassium salicylate, which when heated with alkyl halogens yield alkyl derivatives such as methyl methyl salicylate, $C_6H_4(OCH_3)COOCH_3$. If dialkyl compounds of this type are hydrolyzed with alcoholic potash, only the alkyl of the carboxyl group is removed. The other alkyl group is not removed even on boiling with alkalies, but when heated with hydrochloric acid it is converted into the hydroxy acid.

$$C_6H_4\begin{cases}OCH_3\\COOH\end{cases} + HI = C_6H_4\begin{cases}OH\\COOH\end{cases} + CH_3I -$$

SALICYLIC ACID

Salicylic acid occurs widely distributed in nature in the form of its methyl ester, and this compound forms the greater part of oil of wintergreen or gaultheria and oil of sweet birch. It has been prepared commercially from these oils and the sodium salt of the acid from this source is still preferred by some practitioners instead of that from the synthetic acid. There may have been some reason for this preference in the early days of the synthetic acid, because of the presence of objectionable impurities, but in its present high state of purity it is probable that any supposed difference is due to prejudice, and not to any inherent difference in properties.

Salicylic acid and the salicylates are extensively employed in remedies for rheumatism and gout and to some extent for colds and fever. It is also used in remedies intended for local application in veterinary practice and in corn remedies. Its use as a preservative and an anti-fermentative is well known.

The acid is dispensed alone or in the form of its sodium salt in pills and tablets of different strengths, and combined with morphin sulphate. It is combined with sodium bicarbonate, colchicin, and guaiac in rheumatism tablets; with sodium sulphate, Nux Vomica, ipecac, and Capsicum in anti-fermentative tablets; and with astringent drugs for leucorrhea. Elixir of Salicylic acid compound contains also Cimicifuga, Gelsemium and potassium iodide and it will be found in cough mixtures containing eriodictyon, licorice, wild cherry, potassium bromide, Grindelia, and tar.

Sodium salicylate is a component of many different tablet compounds. It will be found with acetanilid, acetphenetidin, codein, caffein, and sodium bicarbonate in remedies of the headache and cold type; also with Hyoscyamus, camphor monobromated, acetanilid and Gelsemium for migraine; in rheumatism mixture with colchicin, codein, and Digitalis; with aconite, belladonna, bryonia, morphin, mercuric iodide, and oil of gaultheria for follicular tonsillitis; with eucalyptol, thymol, and menthol and sodium benzoate, borate, bicarbonate, and chloride in nasal tablets; and with ginger, Capsicum, and cardamom in anti-fermentative mixtures.

Sodium salicylate is used in liquid rheumatism remedies with the salicylates of potassium and lithium and manaca, and also with colchicin.

Bismuth salicylate is a basic salt used for intestinal catharrh, and will sometimes be encountered in tablet form alone, and with zinc sulphocarbolate and aromatics.

Salicylic or ortho hydroxybenzoic acid occurs in white needle-like crystals, melting 156°, subliming at the temperature of the water-bath and volatile in a current of steam. It is slightly soluble in cold water, readily on warming and dissolves in all the ordinary organic solvents. Its neutral solution gives an intense violet color with ferric chloride, it gives a precipitate of tribromphenol bromide with bromin water which on filtering, treating with sodium bisulphite and washing yields tribromphenol melting 92.5–93.5, and from a solution alkaline with soduim carbonate, a violet-red precipitate of tetraiodophenylenquinone, $(C_6H_2I_2O)_2$, with iodin in potassium iodide. Silver nitrate and lead acetate give precipitates with neutral salicylates, but not with the free acid. Barium chloride does not give a precipitate. Fehling's solution is reduced by the acid.

The para and meta hydroxybenzoic acids isomeric with salicylic have different melting-points and do not give the violet color with ferric chloride. The para melts 213–214° and the meta 200°. They are but sparingly soluble in chloroform.

Alkaline solutions of salicylic acid give a precipitate of the acid when acidified with mineral acid, and on shaking with ether it is entirely dissolved. It is partially removed from its acid solution by petroleum ether, but if the amount is large this solvent seems incapable of removing the entire quantity, even after several shake-outs. The first two or three shakings remove noticeable quantities, but after this the successive shakings seem to have little effect.

Salicylic acid may be removed from an ether solution by shaking with sodium bicarbonate, differing in this respect from phenol and furnishing a means of separation.

Para-creosotic acid is about the only acid which is likely to be found in salicylic acid, and its presence will be indicated by a lowering of the melting-point.

If .25 gram of the acid is triturated with 5 mils of water and poured into a test-tube, treated with 2 drops of 2 per cent alcoholic solution of furfuraldehyde, shaken, and then 2 to 3 mils of concentrated sulphuric acid poured carefully to the bottom of the tube, a brown zone appears if *o*-creosotic is present, and a violet zone if phenol or *m*- and *p*-creosotic acids are present.

One gram of salicylic acid dissolved in 5 mils water and 1 mil nitric acid 1.2 sp. gr. and boiled five minutes, forms nitro salicylic acid, which may be precipitated by pouring into 20 mils water and purified by recrystallization from hot water. The nitro acid sinters at 220 and melts at 226°, and serves as a means of identification.

Fuming nitric acid converts salicylic acid to picric acid.

Salicylic acid dissolves in formaldehyde solution and on adding concentrated sulphuric acid a precipitate is obtained, colorless at first, but becomes red and the solution magenta.

A solution of salicylic acid or a salicylate treated with sodium nitrite, acetic acid, and a drop of copper sulphate and boiled gives a blood red color. Benzoic and cinnamic acid do not give this test.

When carried out in the following manner Jorissen's test is stated to be considerably more delicate than the ferric chloride reaction. The solution to be tested is treated with 4 to 5 drops of 10 per cent solution of sodium or potassium nitrite, 4 to 5 drops of 50 per cent acetic acid, and 1 drop of a 1 per cent solution of copper sulphate, the liquid being shaken after the addition of each reagent. After heating in a boiling water-bath for forty-five minutes and cooling the color is examined against a white background, a blank test being carried out in a similar manner. In this way .005 to .01 mg. of salicylic acid in aqueous solution can be detected: faint but perceptible reactions are obtained with 5 to 8 mils of a 1 : 1,000,000 solution, and with 18 to 25 mils of a 1 : 3,500,000 solution. The ferric chloride and Jorissen reactions may be applied to the same solution of salicylic acid, the liquid, after the addition of ferric chloride, being diluted until the violet color disappears and then submitted to the Jorissen test. Benzoic, cinnamic, and tartaric acids, maltol, isomaltol, orcinol, arbutin, resorcinol, and phlorizin do not respond to the Jorissen test. A 1 : 100,000 solution of phenol gives the same color as a 1 : 1,000,000 solution of salicylic acid. With the Millon reagent phenol can be detected at a dilution of about 1 : 2,000,000. With saligenin the limit of delicacy of the ferric chloride reaction is between 1 : 10,000 and 1 : 20,000; in the Jorissen test saligenin gives a red color at 1 : 10,000, a yellowish tint at 1 : 100,000, and no reaction at 1 : 1,000,000. 2-hydroxyisophthalic acid gives the Jorissen reaction up to a dilution of 1 : 100,000, but is easily distinguished from salicylic acid by the color

it gives with ferric chloride. Methyl-ethyl acetoacetate gives neither the Millon nor the Jorissen reaction at a dilution of 1 : 1000.

The mono-metallic salts are prepared by neutralizing a hot aqueous solution with metallic carbonate and are as a rule soluble in water. The dimetallic salts are obtained by employing an excess of metallic hydroxide and, with the exception of the alkali salts, are insoluble. The dimetallic salts are decomposed by carbon dioxide with formation of the mono-metallic salts.

In the general scheme of analysis salicylic acid appears first on shaking out the acid solution with petroleum ether, and will be indicated on testing the residue with ferric chloride. If benzoic acid is present it can be separated by precipitating the salicylic acid with bromin water and the identity of the tribromphenol established by washing, drying, and determining its melting-point.

If the acid or its salt occurs alone in a product or in a mixture where it is the only substance removable from acid solution by ether, its determination is simple. Tablets in sufficient quantity, usually 5 to 10, should be introduced into a separator, a little water added until they are disintegrated, diluted, sulphuric added to render the solution distinctly acid and the salicylic acid extracted with ether, using three shakeouts. The combined ethereal solutions are then washed with water, filtered through a dry filter into a tared beaker, washing out separator and filters with more ether, and the solvent evaporated using a fan and then dried in a vacuum desiccator and weighed.

Liquids should be acidified with sulphuric acid and the salicylic acid shaken out precisely as above. In some cases it is advisable to shake the acid back into an alkaline solution with dilute sodium hydroxide, and after collecting the alkali in another separator the salicylic acid is liberated by sulphuric acid, and shaking out with ether and determined as above.

Salicylic acid can be titrated directly with alkali, using phenolphthalein 1 mil N/10 alkali = .0138 gram acid.

In cases where the acid occurs mixed with benzoic acid, the combined acids should be shaken out, dried in vacuum and weighed. The residue is then dissolved in about 2 to 5 mils alcohol, diluted with dilute hydrochloric acid, bromin water added in excess, the flask stoppered and allowed to stand until the tribromphenol bromide has settled and the liquid is clear. The mixture can then be filtered through a Gooch, the excess of bromin boiled off from the filtrate and the benzoic acid shaken out with chloroform and determined, or the tribromphenol bromide in the Gooch can be washed with sodium bisulphite solution followed by water, and then dried *in vacuo* and weighed as tribromphenol.

DETERMINATION OF SALICYLIC ACID BY BROMIDE BROMATE METHOD DESCRIBED IN DETAIL IN THE NEW EDITION OF ALLEN

The process is as follows: A known weight of the sample is dissolved in water (preferably with the aid of a little sodium hydroxide) and a volume corresponding to about .100 gram of salicylic acid diluted to about 100 mils with water in a stoppered bottle. Ten mils of hydrochloric acid (sp. gr. 1.1) is next added (von Genersich states that it is preferable to add the salicylic acid solution to the bromate solution *after* the acidification of the latter), followed by a known volume (about 50 to 60 mils) of a solution containing sodium bromate and bromide, of which sufficient should be used to give about 75 per cent of bromine in excess of that entering into the reaction.[1] The bottle is closely stoppered, well shaken, and allowed to remain in the dark for at least one hour to ensure the completion of the reaction.[2] Another bottle containing an equal quantity of the bromin solution is similarly diluted and acidified, and left to stand side by side with the sample. A solution of potassium iodide (10 per cent) is next added to the contents of both bottles, and the liberated iodine titrated with a decinormal solution of sodium thiosulphate (24.827 grams of $Na_2S_2O_3+5H_2O$ per liter). Each 1 mil of this thiosulphate solution required represents .008 gram of bromin in excess of that which has reacted with the salicylic acid, .138 gram of which cause the disappearance of .480 gram of free bromin, or as much as will be liberated by about 50 mils of the bromin solution. The observation of the end-point may be assisted by the use of starch paste, but it is important that this should not be added until the liquid is nearly decolorized. Hence, if a preparation already containing starch is to be examined, the salicylic acid must first be extracted by alcohol or other suitable solvent, and the process applied to the solution. In the case of wine and beer, the salicylic acid should be first extracted by the use of a mixture of ether and light petroleum, and the process applied to the aqueous liquid obtained on shaking the above solution with sodium hydroxide.

A. Seidell[3] has made an exhaustive study of the determination of salicylates by the bromin method of Freyer[4] which is essentially the Koppes-

[1] This solution is prepared by dissolving 19.5 grams of bromin (=6.5 mils) in about 100 mils of water containing 10 grams of sodium hydroxide. The liquid thus obtained is boiled well, and then diluted with water to 2 liters. The solution keeps indefinitely. On addition of hydrochloric acid, the whole of the bromin present is liberated accordin to the equation:

$$5NaBr+NaBrO_3+6HCl=6NaCl+3Br_2+3H_2O$$

[2] A more prolonged standing is desirable when very accurate results are required.

[3] J. Am. Chem. Soc., 1909, 1168; Am. Chem. Jour., 1912, 508.

[4] Chem. Ztg., 1896, 20, 820.

chaar method, and by the iodin method of Messinger and Vortmann [1] and concludes that the results obtained were not satisfactory or of uncertain reliability. At the time of his second investigation he was engaged in evolving a satisfactory method for determining thymol, and he finally accomplished his purpose and showed further that the method was applicable for estimating salicylic acid.

The details of the method as finally elaborated are as follows: The weighed sample of .1 to .5 gram of thymol or salicylic is placed in a 300-mil glass-stoppered bottle with 1 to 2 mils carbon tetrachloride and 100 mils water. Bromin vapor is then poured into the mixture until the color, after thorough shaking, shows that considerable excess of bromin is present. After one-half hour 5 mils of carbon bisulphide and immediateately thereafter 5 mils of aqueous 20 per cent potassium iodide solution are added and the liberated iodin corresponding to the free excess of bromin is titrated with .1/N thiosulphate; an additional amount of potassium iodide solution is added and if no further liberation of iodin occurs the reading on the burette is taken. Five mils of aqueous 2 per cent potassium iodate solution are then added and after thorough shaking the titration with thiosulphate is continued until the iodin color is just discharged for the second time. The completion of the reaction is tested by further addition of potassium iodide and iodate solutions. The difference between the first (which should be from about 5 to 15 mils .1/N thiosulphate) and the second readings corresponds to the hydrobromic acid formed by the action of bromin on the thymol. The calculation is made on the basis of two molecules of hydrobromic acid per molecule of thymol; 1 mil .1/N thiosulphate is, therefore, equal to .0075056 gram thymol, or .006883 gram salicylic acid.

W. O. Emery [2] has obtained excellent results by weighing the tetraiodophenylenequinone obtained by precipitating a solution of salicylic acid in excess of sodium carbonate by iodin. This method may be employed in separating salicylic acid from cinnamic acid, and Emery gives in detail two procedures to be employed in working with liquid and solid headache mixtures, and these have been grouped with several others, in the chapter on acetanilid, acetphenetidin, etc. The details in so far as they apply to salicylic acid are as follows: The acid after separation from other substances by appropriate means, is manipulated into chloroform solution, and run into a 200-mil Erlenmeyer containing 10 mils water and 1 gram dry sodium carbonate, sufficient to fix all the salicylic acid present, and distilled over a small flame until the chloroform has been expelled. The aqueous solution is transferred to a liter flask, treated with 10 grams of dry sodium carbonate, and made up to the mark,

[1] Ber. Chem. Ges., 1890, 23, 2753.

[2] U. S. Dept. Agri. Bu. Chem., Bull. 152, 1911, 236; Ibid., Bull. 162, 1912, 195.

100-mil aliquots are transferred to 200-mil Erlenmeyers, heated nearly to boiling, 35 mils of N/5 iodine in potassium iodide added (or double this quantity of N/10 iodin) enough to ensure an excess of iodin. The mixture is heated on the steam-bath at nearly boiling temperature for one hour, during which time a violet-red precipitate of tetraiodophenylequinone $(C_6H_2I_2O)_2$, will appear. The excess of iodin is removed by a few drops of sodium thiosulphate, and the liquid decanted through a tared Gooch, care being taken that most of the precipitate remains in the flask. The precipitate is treated with 50 mils boiling water, digested ten minutes, poured into the Gooch, and the balance of the precipitate washed out with hot water. It is then dried to constant weight at 100°. The weight of the substance multiplied by .4654 gives the amount of sodium salicylate.

Sodium salicylate is the most important medicinal salt of salicylic acid. It should be readily and completely soluble in water, and on adding hydrochloric or sulphuric acid, the acid is precipitated and may be removed by ether. The acid can be determined by this method, or by the bromide-bromate or iodin methods.

Some firms make a specialty of selling a product made from the acid obtained from oil of wintergreen. This is often called " Sodium Salicylate true " and other designations to distinguish it from the salt made with synthetic acid. There is no way of distinguishing between the two if they are both pure, but, if in separating the acid, it is found contaminated with cresotic acid it is evident that the synthetic product was used to make the salt. A negative test, however, signifies nothing. Some products have a suggestion of wintergreen odor, but this also is no proof that the salt was prepared from natural oil.

Potassium and lithium salicylate have a limited use in medicine and basic bisumuth salicylate and basic mercury salicylate will be encountered. Didymium salicylate is called dymal.

Alkaloidal salts of salicylic acid used commercially include antipyrin salicylate known as salipyrin, hexamethylenetetraamine salicylate, and phenocoll salicylate or salocoll.

DERIVATIVES OF SALICYLIC ACID

The ingenuity of the manufacturer of pharmaceuticals has resulted in the production of vast numbers of derivatives of salicylic acid.

In this list which follows the derivatives have been divided with respect to the molecular change in the original acid. Those where the change affects the nucleus alone are placed together, those where the hydroxyl is esterified are assigned to another group, and so on.

The first group consists really of substituted acids, and the chemical

properties of these are in a general way similar to those of the parent substance.

The second group consists of acids possessing a free carboxyl group, but with a substituted hydroxyl. These acids are removed from their solutions in ether by caustic alkalies and bicarbonates, but are very sparingly soluble in water, and the aqueous solution does not give any reaction with ferric chloride until it has been boiled and cooled.

The third group is made up of alcoholic esters containing the free phenolic hydroxyl of the original acid. They are all removed from their ether solution by caustic alkalies, but are not taken out by bicarbonates. The aqueous solution gives colorations with ferric chloride in the cold. When saponified with alcoholic potash they yield sodium salicylate and an alcohol. If the alcohol is volatile it can be distilled off from the alkaline solution, mixed with the ethyl alcohol of the reagent, and then separated and identified.

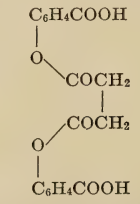
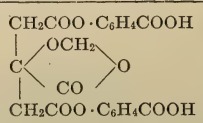
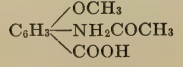
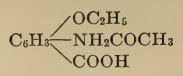
The members of the fourth group, which includes esters with phenols instead of alcohols, resemble those of the third in their actions toward alkalies and bicarbonates. They are much less soluble in water, and on hydrolysis with alcoholic potash yield salicylic acid and a phenolic compound. The alkaline solution may be evaporated until the alcohol has been driven off and then the residue transferred to a separator, acidified, and shaken with ether, which will dissolve both the salicylic acid and the phenol; on separating the solvent and shaking it first with sodium bicarbonate solution and then with sodium hydroxide, the acid will pass into the bicarbonate and the phenol into the alkali. The two alkaline solutions can then be acidified separately and the acid and phenol shaken out with ether and obtained in a condition for identification.

The fifth group is relatively small and contains those substances in which both the hydroxyl and the carboxyl groups are esterified. They are of course indifferent to either caustic alkali or sodium bicarbonate when dissolved in ether, and are thus readily differentiated from any of the preceding substances. When hydrolyzed with alcoholic potash they yields acids, alcohols, and phenols depending on their composition, and which may be detected as described in the preceding paragraphs.

SUBSTITUTED ACIDS, $C_6H_x\begin{matrix}OH\\COOH\end{matrix}$

Individual.	Formula.	Common Names.	M. pt.	Solubility in			Color with Ferric Chloride.	Uses.
				Water.	Alcohol.	Ether.		
Monoiodo-salicylic acid	$C_6H_3I \cdot OH \cdot COOH$		198°	Slightly	Sol.	Sol.		Antirheumatic
Bismuth salt of monoiodo-salicylic acid (yellow powder		Iodylin						Substitute for Iodoform
Diiodosalicylic acid.....	$C_6H_2I_2 \cdot OH \cdot COOH$		220°–30°		Sol.	Sol.		Antirheumatic, antiseptic, analgesic, antipyretic
Sodium diiodosalicylate...	$C_6H_2I_2 \cdot OH \cdot COONa \cdot 5H_2O$			Sol.				Same used in parasitic skin diseases
Methyl diiodosalicylate...	$C_6H_2I_2 \cdot OHCO \cdot OCH_3$	Sanoform	110°		Sol.	Sol.		Antiseptic and deodorant in syphilis; ulcers, etc.
Ethyl diiodosalicylate....	$C_6H_2I_2 \cdot OH \cdot COOC_2H_5$		132°	Sl. sol.	Sol.	Sol.		Substitute for Iodoform
Dithiosalicylic acids, two forms	$(C_6H_3OH \cdot COOH)_2S_2$							
Sodium salt.....		Dithion						Mixture of salts of both forms for foot and mouth disease
Bismuth salt.....	Contains 72% Bi_2O_3	Thioform						Substitute for Iodoform
Amido salicylic acid (meta)	$C_6H_3 \cdot {}^{1}COOH \cdot {}^{2}OH \cdot {}^{5}NH_2$ meta							
Amied salicylic acid(ortho)								Antirheumatic
Salicyl sulphonic acid....	$C_6H_3SO_3H \cdot OH \cdot COOH$		120°	Sol.		Sol.	Violet	Antirheumatic. Reagent for albumen
Sodium salt.....				Sol.	Almost insol.	Almost insol.		Antiseptic, antirheumatic, antipyretic

ACIDS WITH OH ESTERIFIED AND THEIR DERIVATIVES, $C_6H_4\begin{cases}OX\\COOH\end{cases}$

Acetyl salicylic acid.....	$C_6H_3OC_2H_3O\cdot COOH$	Aspirin	132°–135°	Very slightly soluble	Soluble	Soluble	No color at first, gradually on standing	Antirheumatic, antipyretic, analgesic
Salicylic acid methylene acetate (reaction product of acetyl salicylic acid and formaldehyde)		Indoform	108°–109°	Slightly cold Readily hot				Intestinal antiseptic
Succinyl disalicylic acid.....		Diaspirin	168°–178°	Almost insol.	Slightly sol.			Diaphoretic, antirheumatic
Methylene-citryl salicylic acid		Novaspirin		Spar. soluble	Soluble	Spar. soluble		Antirheumatic, antipyretic, analgesic
Acetamido - methyl salicylic acid		Benzacetin	205°	Slightly sol.	Soluble			Substitute for Salol
Acetamido-ethyl salicylic acid		Reported also as Benzacetin	189°–190°					

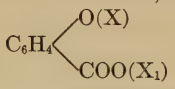
ESTERS WITH ALCOHOLS AND THEIR DERIVATIVES, $C_6H_4\begin{matrix}OH\\COO(X)\end{matrix}$

Methyl salicylate	$C_6H_4OH \cdot COOCH_3$	Oils of Gaultheria and Betula (Wintergreen and Birch)	Boils 219°–221°	Slightly Sol.	Soluble	Soluble	Antirheumatic and antiseptic
Methyl dibrom salicylate	$C_6H_2Br_2OH \cdot COOCH_3$	Salibromin		Insoluble			Antirheumatic, intest. antiseptic, antipyretic
Diodomethyl salicylate	$C_6H_2I_2OH \cdot COOCH_3$	Sanoform	110°–110.5°		Soluble	Soluble	Antiseptic and deodorant
Ethyl salicylate	$C_6H_4OH \cdot COOC_2H_5$		Boils 231°	Slightly sol.	Soluble	Soluble	
Benzyl salicylate			Boils 208°				Antiseptic for external use
Salicyl salicylate	$C_6H_4OHCOOC_6H_4COOH$	Diplosal	147°–148°	Almost insol.		Soluble	Antirheumatic, antiseptic, and antipyretic
Bromyl salicylate							
Santalol salicylate	$C_6H_4OH \cdot COOC_{15}H_{23}$	Santyl	Boils 121°–126° 2 min. pressure	Insoluble	Soluble	Soluble	Antirheumatic and antiseptic
Monosalicylic acid glycerin ester	$C_6H_4OH \cdot COOC_3H_5(OH)_2$	Glycosal	76°	Soluble	Soluble	Slightly sol.	Antiseptic and antirheumatic
Salicylic acid glycerineformaldehyde ester	$C_6H_4OH \cdot COO$ $CH_2CHO(CH_2O)=CH_2$	Protosal	Boils 200°				Antirheumatic
Monoglycol salicylate	$C_6H_4OH \cdot COO(CH_2CH_2OH)$	Spirosal	Boils 169°–170° at 12 min.	Soluble	Soluble	Soluble	Externally in rheumatism mixed with oils
Mixture of methyl and ethyl glycollic esters of salicylic acid		Salen			Soluble	Soluble	Same as spirosal
Methyl oxymethyl salicylate	$C_6H_4OHCOO(CH_2OCH_3)$	Mesotan Ericin	Boils 162°	Sl. sol.	Sol. Sol.		Antirheumatic externally
Acetal salicylate	$C_6H_4OH \cdot COOCH_2COCH_3$	Salacetol	71°	Sl. sol.	Sol. Sol.		Antirheumatic antiseptic
Salicylamide	$C_6H_4OH \cdot CONH_2$		138°	Sl. sol.	Sol. Sol.		Antiseptic, analgesic, antipyretic

ESTERS WITH PHENOLS AND LIKE SUBSTANCES, AND THEIR DERIVATIVES

Acetonyl salicylate.....	$C_6H_4OH \cdot COOCH_2COCH_3$	Salacetol, Salantol	71°	Very sl. sol.	Sol. Hus.		Substitute for salol
Phenyl salicylate	$C_6H_4OH \cdot COOC_6H_5$	Salol	42°–43°	Very slightly Sol.	Soluble	Soluble	Antiseptic, antipyretic, analgesic
Chlorophenyl salicylate...	$C_6H_4OHCOOC_6H_4Cl$	Chlor salol					
Acetyl paramidophenyl salicylate	$C_6H_4OH \cdot COOC_6H_4$—$NHCOCH_3$	Salophen	187°–188°	Insoluble	Soluble	Soluble	Antiseptic antipyretic
Tribromsalol.....	$C_6HBr_3OH \cdot COOC_6H_5$	Cordol	195°	Insoluble	Sl. sol.	Slightly sol.	Intestinal antiseptic
Cresol salicylate, three forms	$C_6H_4OHCOOC_6H_4CH_3$	Ortho cresalol Meta cresalol Para cresalol	35° 74° 39°	Insoluble	Soluble	Soluble	Ortho not used medicinally. Meta and para used as substitute for salol
Xylenol salicylate, three forms	$C_6H_4OHCOOC_6H_4(CH_3)_2$						
Thymol salicylate.....	$C_6H_4OHCOOC_6H_3(CH_3)C_3H_7$	Salithymol		Slightly sol.	Soluble	Soluble	Intestinal antiseptic
Guaiacol salicylate.....	$C_6H_4OHCOOC_6H_4OCH_3$	Guaiacol salol	65°	Insoluble	Soluble	Soluble	Intestinal antiseptic, antirheumatic
Creosote salicylate.....		Salocreol					
Alpha-naphthol salicylate..	$C_6H_4OHCOOC_{10}H_7$	Alphol	83°	Insoluble	Soluble	Soluble	Intestinal antiseptic, antirheumatic
Beta-naphthol salicylate...	$C_6H_4OHCOOC_{10}H_7$	Betol or salinaphthol	95°	Insoluble	Soluble	Soluble	Intestinal antiseptic, antirheumatic

ESTERS INVOLVING BOTH OH GROUPS, AND THEIR DERIVATIONS



Acetyl methyl salicylate....	$C_6H_4(OCOCH_3)(COOCH_3)$	Methyl Aspirin 54°	Insol.	Sol.	Sol.	Antineuralgic
Methyl benzoyl salicylate....	$C_6H_4(OCH_3)(COO(C_6H_3CO))$	Benzosalin 85°		Sol.		Intestinal antiseptic.
Acetyl phenyl salicylate....	$C_6H_4(OCOCH_3)(COOC_6H_5)$	Vesipyrine Acetyl Salol 97°	Insol.	Sol.		

MISCELLANEOUS

Salicyl-α-methyl phenyl-hydrazone.....	$C_6H_5CH_3N \cdot N \cdot CH \cdot C_6H_4OH$	Agathin 74° Cosmin	Insol.	Sol.	Sol.	Antirheumatic, antineuralgic
Salicyl-quinin..	$C_6H_4OHCOOC_{20}H_{23}N_2O$	Saloquinine 130°	Insol.	Sol.	Sol.	Antineuralgic, antiperiodic, analgesic, febrifuge
Salicyl quinin salicylate....		179°	Sl. sol.			Antineuralgic, antirheumatic
Condensation product of salicylic and gallic acids...	C_6H_4OH, $COOCOC_6H_2(OH)_3$	Salitannol 210°	Insol.	Spar. Sol.	Insol.	Substitute for salol
Condensation product of salicylic and boric acids...	$(C_6H_4OCOOH)_2BOH$	Borosalicylic acid				Antiseptic

Phenyl Salicylate

$C_6H_4OHCOOC_6H_5$

Salol

Salol is used as an intestinal antiseptic and occurs alone in tablets and in powders and mixed with bismuth subnitrate, subcarbonate and subgallate, calomel, sodium bicarbonate, zinc sulphocarbolate, and pepsin. It is employed in typhoid fever and in some forms of dyspepsia and

bowel trouble, as chronic constipation. It is often dispensed with acetanilid, acetphenetidin, lactophenin, and other anilides and phenetidins.

It is a compound of many gonorrhea mixtures with sandalwood oil, copaiba, oleoresin of cubeb, and pepsin.

It is sometimes used externally as an antiseptic for sores and wounds.

Salol is a white crystalline powder with a faint phenolic odor, melting 42–43° C., almost insoluble in water, soluble in alcohol, ether, chloroform, fixed and volatile oils. Its solution in alcohol gives a violet color when treated with dilute ferric chloride, but if a few drops of the alcohol solution is added to 10 mils of dilute ferric chloride, a white cloudiness, but no color, will be produced on shaking. When warmed with sodium hydroxide it is hydrolyzed, and on diluting with water and acidulating, salicylic acid separates and the odor of phenol will be apparent. The two components can then be readily separated and identified.

Salol can be removed from a solution of ether or chloroform by fixed alkali, and this property furnishes a ready means of separating it from acetphenetidin and other antypyretics with which it commonly occurs.

In order to establish its identity in a mixture of oils, the sample is dissolved in ether, shaken with acid to remove basic constituents, and then extracted with potassium or sodium hydroxide, which will remove the salol. The latter can then be recovered by acidulating and shaking out with ether. If any fatty acids are removed at the same time they can usually be separated from the salol, by shaking the ether solution with sodium bicarbonate, which does not remove the salol.

In order to estimate salol in a mixture of copaiba and other oils, the sample is dissolved in ether, and extracted three times with $2\frac{1}{2}$ per cent sodium hydroxide. The alkaline solution is brought to the temperature of the steam-bath and held for five to ten minutes, and the balance of the determination conducted according to the following process:

C. C. LeFebvre [1] has applied the bromin method to the determination of salol in tablets and powders:

First extract the salol from a weighed portion of the powdered sample by means of 50 mils ether. In order to prevent moisture from collecting on the paper, use a short extraction thimble in an ordinary extraction tube, the ether being introduced by means of a separatory funnel, the stem of which passes through a stopper in the end of the tube. Run the solvent into a flask and remove the solvent by air blast. Then add 10 mils $2\frac{1}{2}$ per cent sodium hydroxide and heat for five minutes at the temperature of the steam-bath. After this is complete dilute the alkaline liquid to about 200 mils, add an excess of potassium-bromide bromate solution, followed by 10 mils of concentrated hydrochloric acid. Shake the mixture for a minute, and then frequently during a half hour. At the end

[1] U. S. Dept. Agri. Bu. Chem. Bull. 162, p. 203.

of this time add 10 mils of a 15 per cent potassium-iodide solution, and frequently agitate the mixture while it reacts for fifteen minutes. Titrate the free iodin with the thiosulphate solution which has been standardized against the bromin solution. From the number of cubic centimeters of the bromin solution expended, calculate the salol on the basis of 12 atoms of bromin to 1 molecule of salol.

A few determinations made, where various excipients were added to the salol before saponification and allowed to remain throughout the titration, indicate that none of them except lactose interferes to any considerable degree. Even in this case, the quantity usually present would not throw the result off more than a few per cent. Tragacanth, Indian gum, acacia, lactose, starch, and dextrin were tried. This would seem to show that the method may be carried out directly on salol in the tablet, without previous extraction with ether.

The reactions involved are the following:

First, the salol is saponified to sodium or potassium salicylate and phenolate:

$$HOC_6H_4CO \cdot OC_6H_5 + 3KOH = KOC_6H_4CO \cdot OK + C_6H_5OK + 2H_2O$$

Phenol is attacked by bromin in excess to form symmetrical tribromophenolbromid:

$$C_6H_5OH + 4Br_2 = C_6H_2Br_3OBr + 4HBr$$

Salicylic acid also forms the same product, inasmuch as the tribromosalicylic acid first formed is very unstable and loses its carboxyl:

$$C_6H_2Br_3OBr + 2HI = C_6H_2Br_3OH + HBr + I_2$$

As a result, 12 atoms of bromide have been used up by 1 molecule of salol.

The procedure for assaying mixtures of acetphenetidin and salol is described on page 859.

Acetyl paramino phenylsalicylate

$$C_6H_4OH \cdot COOC_6H_4NHC.OCH_3$$

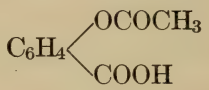
Salophen

It forms small, white, crystalline leaflets or powder, odorless and tasteless, melting at 187 to 188° C., and containing 51 per cent of salicylic acid. It is almost insoluble in cold water, more soluble in warm water, but freely soluble in watery solutions of the alkalies and in alcohol, ether, and benzene, but not in petroleum benzine.

If its alkaline solution be boiled it gradually becomes blue; on continuing the boiling the color is discharged, but is again produced on cooling

and exposure to air. On addition of ferric chloride to the alkaline solution the violet color characteristic of salicylic acid is produced, but a simple aqueous solution of salophen does not react with ferric chloride and should not be changed by silver nitrate.

Acetyl salicylic acid



Aspirin

Aspirin forms small, colorless, crystalline needles, melting at 129–130°, odorless, and having an acidulous taste. It is soluble in 100 parts of water and freely soluble in alcohol, ether, chloroform, and glacial acetic acid. It is readily split up on boiling with water or with alkalies with the production of acetic acid and salicylic acid or a salicylate.

It forms clear, colorless solutions with water, which do not develop a violet color on the addition of ferric chloride unless previously boiled or hydrolyzed by boiling with sodium hydroxide, or unless it stands for some time in the presence of cold water. It gives no reaction with silver nitrate, and should leave no residue when heated on platinum foil.

When added to boiling water the odor of acetic acid is easily distinguished.

Acetyl salicylic acid may be removed from chloroform with alkalies and by sodium bicarbonate. If the former is used there may be a certain amount of hydrolysis and free salicylic acid results, but with bicarbonate in ice-cold solution the hydrolysis can be kept down to a minimum.

Acetyl salicylic acid does not give a precipitate with bromin water, hence it is easy to detect the presence of free salicylic acid. Dissolve in alcohol, add a few drops hydrochloric acid, then bromin water until a permanent yellow color is obtained. If salicylic is present, the color of bromin will disappear at first, but no color will appear until dilution has reached a certain degree and finally the color of bromin persists and a precipitate agglomerates and settles. If acetyl salicylic is alone present, the color due to bromin does not disappear and no precipitate appears on dilution.

Astruc finds that acetyl salicylic acid can be titrated accurately in dilute alcoholic solutions with potassium hydroxide and phenolphthalein without splitting off any of the acetyl group. From the acid number and saponification number the quality of commercial samples can be determined.

Dr. Emery found that aspirin of 100 per cent purity softened at 129.5° C. and melted from that temperature up to 130°. Mixtures of the pure substance with salicylic acid showed a tendency to soften several degrees

below the melting-point, in some cases 10–20°, the material then remaining in a more or less pasty condition until the point of complete fusion is reached, which in the case of mixtures containing 60–85 per cent of salicylic acid extends over about 10°, the acid not dissolving readily in the melt, but remaining in solid form at the bottom and sides of the capillary. A mixture containing 58 per cent of aspirin melts sharply 115–116°, indicating an eutectic mixture of about that composition.

The estimation of free salicylic acid in acetyl salicylic acid may be accomplished by dissolving .1 gram of the sample in 1 mil of alcohol, followed by 48 mils of water and 1 mil of ferric chloride solution (1 volume of test solution U. S. P. to 100 volumes of water). The color is then matched against that produced by known amounts of a standard solution of sodium salicylate (.116 gram to 1 liter) made up to the same volume, and using the same quantity of reagent.

Methyl Salicylate, C_6H_4 OH·COOCH$_3$

Methyl salicylate is an exceptionally interesting substance, both on account of its varied uses, and the anomalous commerical conditions relating to it. It is used to a large extent as a flavoring agent, as an antiseptic and as an antirheumatic. In the trade it is sold under three names with widely divergent prices, depending on the designation.

Methyl salicylate is widely distributed in nature, but is especially prominent in the leaves and the fruit of the wintergreen (Gaultheria procumbens) and in the stems and bark of the sweet birch (Betula lenta).

also occurs in senega root (Polygala senega), Gaultheria punctata, and G. leucoceupa, and in small quantities in other plants. It probably is combined with other substances in the plant, but in a state where it is readily set free by the action of ferments, heat or water.

The pleasant taste of the wintergreen plant probably first suggested its use in the form of an extract or essence for flavoring purposes, and, as the commerce grew and with it a demand for a purer product, the highly rectified oil containing the essential flavoring agent was gradually evolved. Owing to the increasing demand for the oil, and the comparatively limited amount of the plant, the hunt for other sources of crude material was started, and the oil distilled from sweet birch came into the trade. Finally the chemical composition of the oil was established as methyl salicylate, and after synthetic salicylic acid came to be a commercial possibility, it was but another step to prepare the methyl ester, and the latter is now made in a large way.

After salicylic acid was found to have a physiological and therapeutic importance, the medical profession seemed to prefer the natural product to the synthetic, but later, when processes of manufacture became more

refined and no chemical difference existed between the two, this prejudice began to wane.

The oil prepared from wintergreen and rectified contains a small quantity of a mixture of substances which appear to give it a shade of flavor differing slightly from the ester made directly from salicylic acid, and the same possibly applies to the oil from birch, though to a much less extent. The condition as regards the flavor is probably analogous to that existing between what is known as straight and rectified whisky. Chemically, these three products are practically the same, the wintergreen oil being the less pure. The anomalous condition is manifested forcibly in the price, for wintergreen sells for $6 to $7 per pound, birch for $5.50 to $6, and the synthetic for about $0.65 to $0.70.

In the trade the following classifications are in vogue: oil of wintergreen leaf, oil gaultheria prepared from Gaultheria procumbens and now practically off the market: oil betula, oil of wintergreen from Betula lenta: methyl salicylate, synthetic or artificial oil of wintergreen.

In a chemical sense, all of these terms are practically synonymous, and in the last edition of the Pharmacopœia they are all grouped together under the one heading Methyl Salicylate.

Some oils will be encountered having a red color, which has been attributed to iron, but it is doubtful if that metal is responsible for the coloration. If a red oil is dissolved in ether and shaken with dilute potassium hydroxide and the resultant alkaline solution neutralized, a colorless oil will be obtained. It is probable that the color is due to the same cause which produces a pink tint in phenol when it has stood for some time and which has been conclusively proven to be due to other causes than iron.

Power and Kleber investigated the oils of gaultheria and betula, with special reference to the products other than methyl salicylate. They found that Gaultheria contained 99 per cent of the ester, and Betula 99.8 per cent. In order to obtain the impurities, the oil was dissolved in ether and shaken with 7.5 per cent aqueous solution of potassium hydroxide to remove the methyl salicylate, leaving the other constituents in the ether. From gaultheria, these constituents were obtained as a semi-solid mass consisting of a paraffin melting 65.5°; an aldehyde or ketone with an odor like oenanthic aldehyde; a secondary alcohol ($C_8H_{16}O$) boiling 160–165°; and an ester which on saponification yielded the above alcohol, and an acid, $C_6H_{10}O_2$. The alcohol and ester possessed the penetrating characteristic odor which gives the peculiar shade of aroma to Gaultheria oil.

From Betula the same constituents minus the secondary alcohol were isolated.

The author had occasion at one time to study the problem of differentiating between the three products, and he came to the conclusion that there was practically no chemical method which would enable the analyst

to assert beyond question that there was any difference. An empirical procedure was used as a makeshift, on account of the practical problem which developed from the use of the oils in which the sample was treated with an excess of sodium hydroxide and left overnight in a stoppered flask. If the odor noticeable was then of a peculiar musty character, the product was deemed to be natural oil, or at least to contain some of the natural product.

At one time there was communicated to me by the Bureau of Chemistry a method of differentiation based on the color given by mixing oil with vanillin and sulphuric acid. It is directed to dissolve 7 drops of the oil in 10 mils of a 5 per cent alcoholic solution of vanillin, and on the addition of 1 mil concentrated sulphuric acid, a dark red color appears in the case of oil of Gaultheria, changing to blue on the addition of 2 volumes of alcohol. Methyl salicylate gives a yellow color.

I have tried this method with commercial oils and artificial methyl salicylate, and have found that they all react in the same way, all giving the final blue color, changing to a purplish brown after twenty-four hours. Later I experimented with samples of Betula oil according to the procedure of Power and Kleber, and, after recovering that portion of the oil which was not removed by alkali from ether, I tested it according to the vanillin reaction and obtained the same blue color, which in this case was very deep and did not change to purplish brown for several days. It is evident that the color-producing material exists in the impurities, and, from further work done, that it is an unsaponifiable constituent.

For assaying methyl salicylate, the following methods are recommended as giving reliable results.

U. S. P. Assay Method.—Introduce about 2 mils methyl salicylate into a tared flask. Note the exact weight, add 50 mils of half-normal alcoholic potash, connect the flask with a reflux condenser, and heat the mixture on the water-bath during two hours. Then add a few drops of phenolphthalein and titrate the excess of alkali with half-normal hydrochloric acid.

Each mil of N/2 alcoholic potash consumed corresponds to .07603 gram methyl salicylate.

Assay of Methyl Salicylate.—Weigh 1 gram in a closed weighing-tube, and transfer to a 100-mil graduated flask, washing out the weighing tube with alcohol, add 20 mils sodium hydroxide 10 per cent and heat to boiling for two hours. Cool and make up to 100 mils. Remove an aliquot of 10 mils, evaporate any alcohol, transfer to 200-mil Erlenmeyer, add a slight excess of hydrochloric acid, then 1 gram anhydrous sodium carbonate, 100 mils water, and heat nearly to boiling. Add 35 to 50 mils N/5 iodin (approx. standard), digest on steam-bath for one hour, adding iodin from time to time, if necessary Then add a few drops sodium

thiosulphate to destroy the excess of iodin, decant liquid on a tared Gooch, digest precipitate in flask with 5 mils hot water for ten minutes, filter, and wash with hot water, using about 150 mils. Dry and weigh.

Weight $\times .4658 \times .95 \times 10$ = weight of methyl salicylate.

When methyl salicylate occurs in admixtures with other substance of a volatile nature, its determination will depend largely on the nature of the combination. If the other substances are saponifiable to acids capable of ready separation from salicylic acid, the problem is not difficult.

If the sample under examination is a liquid, a measured quantity is transferred to a separator, diluted with water, sodium chloride added, and the soluble oils shaken out with petroleum ether. The solvent, after washing with saturated salt solution is poured into a mixture of alcoholic potash or soda and heated under a reflux for one hour. The alcohol is then removed by evaporation, and the salicylic acid recovered from the alkaline liquid and either weighed or titrated. The methyl salicylate can then be calculated. If other acids are present at this stage, they can be separated by the procedures given under the discussion of salicylic acid.

If the methyl salicylate and salicylic acid occur together in the same mixture, a chloroformic or ethereal solution of the two should be shaken with dilute sodium bicarbonate to remove the acid before attempting to determine the ester.

For the determination of methyl salicylate in flavoring extracts or in spirit of gaultheria, the method of Hortvet and West [1] will be found to give good results.

Measure 10 mils of the extract into a 100-mil beaker, add 10 mils of 10 per cent potassium hydroxide solution, and heat the mixture over a boiling water-bath until the odor of oil of wintergreen has disappeared and the liquid is reduced to about one-half its original volume. By this treatment the methyl salicylate is converted into the potassium salt. Liberate the salicylic acid by the addition of an excess of 10 per cent hydrochloric acid, cool, and extract in a separatory funnel with three portions of 40, 30, and 20 mils of ether respectively. Pour the combined ether extracts through a dry filter into a weighed dish, wash the filter with 10 mils of ether, evaporate filtrate and washings slowly at 50° C., dry one hour in a desiccator, and weigh. The per cent of wintergreen oil by volume (M) is obtainable from the weight of salicylic acid (S) by the following formula:

$$M = \frac{1.101 \times 10 \times S}{1.18}$$

[1] J. Ind. Eng. Chem., 1, 1909, 90.

DERIVATIONS OF HYDROXY BENZOIC ACIDS

Methyl *p*-amido *m*-hydroxy benzoate...	C_6H_3 (OH 3, NH_2 4, $COOCH_3$ 1)	Orthoform	120°	Spar. sol.	Antiseptic, local anesthetic
Sodium Salt of Methyl *p*-amido *m*-hydroxy-benzo-sulphonate...	$C_7H_3O_3(SO_3Na)(NH_2)(CH_3)+H_2O$	Sulphonated Orthoform	269°	Readily sol.	
Methyl *m*-amido-*p*-hydroxy benzoate...	C_6H_3 ($COOCH_3$ 1, OH 4, NH_2 3)	New Orthoform	142°	Somewhat sol.	Antiseptic, local anesthetic

These substances are derivatives of the acids isomeric with salicylic acid. Their properties have been fully described in the chapter on Anesthetics.

COUMARIC ACIDS, $C_6H_4(OH)CH=CH\cdot COOH$

Three forms, known as 1–2, 1–3, 1–4.

The 1–2 form occurs in the leaves of species of Melilotus, sweet clover, and in Angraecum fragrans. It forms colorless crystals, melting 208°, with decomposition. It is freely soluble in water and alcohol, and gives a flourescent solution with alkalies. This acid is converted to salicylic and acetic acids on fusion with potassium hydroxide, but on boiling in alkaline solution it is converted to coumarin. Nascent hydrogen converts it to melilotic acid.

The 1–4 acid occurs as an ester in Cape aloes, in the resin of Picea vulgaris, and is one of the products of hydrolysis of naringin.

Coumarin, $C_6H_4OCOCH=CH$

Coumarin or " Tonka-bean camphor " occurs in Tonka, the seed of several species of Dipteryx, also in the leaves of Liatris odoratissium and those of several other plants.

It forms colorless crystals, melting 67°, with an odor suggestive of vanillin, but nevertheless highly distinctive, recalling freshly mown sweet grass. It is sparingly soluble in cold water, somewhat in cold alcohol, not readily in hot alcohol and in ether.

It is readily distinguished from vanillin as it is not removed from an ethereal solution by caustic alkali.

Melilotic Acid, $C_6H_4(OH)CH_2COOH$

Melilotic acid is 1–2 hydrocoumaric acid, and its close relationship is readily noted by a glance at the formula. It is present with coumarin

in Melilotus officinalis—sweet clover. It melts 82 to 83°, gives a bluish color with ferric chloride, yields acetic and salicylic acids on fusion with potash, and hydrocoumarin $C_6H_4\begin{matrix}CH_2-CH_2\\ \diagdown\!\!\diagup\\ OCO\end{matrix}$ on distillation.

FERULIC ACID, $C_6H_3(OH)(OCH_3)CH=CHCOOH$

Ferulic or *m*-methoxy-*p*-hydroxycinnamic acid occurs in several resins including opoponax and asafetida. It may be obtained from the latter by treating the alcoholic solution with alcoholic lead acetate which precipitates the lead ferulate. The lead salt may then be decomposed with dilute sulphuric acid, and the regenerated acid crystallized out of hot alcohol.

It reduces Fehling's solution and gives a brownish precipitate with ferric chloride, which must not be confused with the buff-colored precipitate obtained with benzoate.

TOLUIC ACID DERIVATIVES

Betanaphthol-Hydroxytoluic Acid

$C_6H_3(OH)(COOH)(CH_2C_{10}H_6OH)$ **2 : 3 : 1**
Epicarin

It forms colorless or yellowish needles, melting at 190 to 195° C., difficultly soluble in water, but easily soluble in alcohol, ether, acetone, and in soaps. It dissolves in oils on the addition of a little ether. It has the character of a strong acid, forming well-crystallized salts, which, however, are sparingly soluble in water, particularly the sodium salt. On exposure to air it acquires a reddish color due to oxidation; if it is then recrystallized from glacial acetic acid, colorless crystals are again obtained which melt at 166° C. These, however, retain a little acetic acid, but lose this by heating at 120° C.

The alcoholic solution of epicarin develops an intense blue color with ferric chloride. When heated with concentrated sulphuric acid, a red-brown solution, having a vivid green flourescence, is produced. If shaken with chloroform and solution of potassium hydroxide, a yellowish color, changing later to yellowish green is developed, thus distinguishing epicarin from beta-naphthol, which produces a deep blue color under the same conditions.

Epicarin is an antiseptic and parasiticide, and is used in the treatment of skin diseases, particularly scabies, and eczema.

Protocatechuic Acid

This acid occurs to some extent naturally both in the free state and in combination. It is obtained on fusing or saponifying some of the resins such as catechu, gum benzoin, gum kino, etc. It forms needle-like crystals melting 195–199°, readily soluble in water, alcohol, ether, and petroleum ether. Its aqueous solution gives a green color with ferric chloride changing to blue and dark red on adding very dilute sodium carbonate. A neutral solution of a protocatechuate gives a violet color with ferric chloride which might be mistaken for the salicylate reactions. Protocatechuic acid gives a precipitate with lead acetate and reduces silver-nitrate on warming.

GALLIC ACID

Gallic or pyrogallol carboxylic acid, $C_6H_2(OH)_3COOH$ 1.2.3.5, is a trihydroxybenzoic acid. It occurs in gall nuts and various vegetable products and is prepared by boiling tannic acid with a dilute acid. It crystallizes in needles with 1 mol. water which melt with decomposition at 220°, pyrogallic acid and carbon dioxide being obtained. It dissolves in water, alcohol, ether, chloroform, and ethyl acetate and its aqueous solution gives a bluish-black color or precipitate, with ferric chloride soluble in excess of the reagent to a green color. The exact color is affected by the concentration of the solution and often the green tint will be the only one obtained due to the small quantity of the sample. It is a strong reducing agent and precipitates gold, silver, and platinum from solutions of their salts.

Gallic acid can be removed from its aqueous acid solution by ether, thus differing sharply from tannic acid.

Gallic acid is used in medicine as an antiseptic and hemostatic. It will be found in foot powders and tablets, in pile remedies, in certain gonorrhea mixtures, and in internal remedies for intestinal hemorrhage, night sweats, hematuria, pyrosis, etc. It is combined with opium and Hydrastis in menorrhagic tablets.

On adding calcium hydroxide solution to a cold concentrated solution of gallic acid, a bluish-white precipitate will form where the test solution is temporarily in excess and will disappear on shaking. When the reagent has been added in excess the precipitate no longer dissolves, and the liquid acquires a tint which is blue by reflected and green by transmitted light, and becomes pink on the addition of a large excess.

With tannic acid the precipitate first formed is pale bluish white and does not dissolve on shaking. It deepens in color when an excess has been added and the solution becomes pinkish with a large excess.

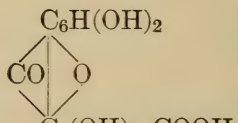
Gallic acid gives no precipitate with gelatin, albumin or the common alkaloids, differing in all these particulars from tannic acid.

Gallic acid is not precipitated from solution by bromin water nor by bromide-bromate reagent. With dilute hydrochloric acid and formaldehyde no precipitate appears at first, but on standing it comes down. Tannic acid reacts in the same way. Gallic acid gives a light-yellow precipitate with lead acetate.

Neither acid can be titrated with alkali.

Though it gives no precipitate with bromin, there is some reaction in solution for on subsequently recovering the acid product with ether, it no longer gives the characteristic color with ferric chloride.

GALLOGEN



Ellagic Acid

is anhydrous ellagic acid prepared from Divi-divi, the pods of Caesalpina coriaria.

It is a yellowish, odorless, tasteless powder, insoluble in all acid and neutral liquids, but soluble in alkaline liquids to the amount of 2 per cent, such solutions being, however, very readily oxidized.

Its solutions in alkaline media give all the reactions of tannic acid with iron salts, gelatin solution, etc. With fuming nitric acid it gives a characteristic dark red color.

Gallogen is an astringent and antidiarrhetic and is used in dysentery, cholera infantum, and diarrhea.

Bismuth subgallate, sometimes called "Dermatol," is a yellowish powder of somewhat variable composition and may yield from 52 to 57 per cent Bi_2O_3 on ignition. It is insoluble in water, alcohol, and ether, but is readily soluble in hot mineral acids and alkali hydroxides, forming with the latter a clear yellow solution rapidly turning red.

If the salt is agitated with hydrogen sulphide water, a black precipitate of bismuth sulphide is obtained, and on filtering and boiling off the excess of hydrogen sulphide from the filtrate, the cooled liquid will give a blue-black color with ferric chloride.

Aluminum gallate, known as Gallal, is soluble in ammonia.

Bismuth oxyiodomethyl gallate or iodogallicin is a dark-gray powder used as a substitute for iodoform.

Galloformin

This substance is a reaction product of gallic acid and hexamethylene tetramine. It is slightly soluble in water, alcohol, ether, and glycerin, and is decomposed by heat. It is used as an antiseptic.

Gallanilide or Gallanol, $C_6H_5NHCOC_6H_2(OH)_3+2H_2O$

Gallanol is a brownish crystalline powder, melting 205° C., soluble in alcohol, ether, and boiling water, insoluble in chloroform and benzol. It is employed externally as an antiseptic and astringent.

Gallicin, or Methyl Gallate

This substance is a grayish-white crystalline powder, melting 202°, soluble in alcohol, ether, and hot water. It is used in eye and throat troubles to relieve inflammation and congestion.

Gallobromol, $C_6Br_2(OH)_3COOH$

Dibromogallic acid is a light-brown powder, melting 140–150° C., soluble in alcohol, ether, and water. It is used internally as a substitute for potassium bromide and externally as an astringent and antiseptic.

Gallotannic Acid

This acid is probably the anhydride of gallic acid, as it is resolved into the latter by boiling with dilute sulphuric acid.

$$C_{14}H_{10}O_9+H_2O=2C_7H_6O_5$$

The pure acid is an almost colorless amorphous substance which dissolves readily in water, alcohol, and glycerin, somewhat soluble in ethyl acetate, and almost insoluble in ether and chloroform. It is removed from its acid aqueous solution to a very slight extent by ether, but is taken up gradually by ethyl acetate, especially if the solution is saturated with salt. Its aqueous solution gives a blue-black precipitate with ferric chloride, with most alkaloids including cinchonin, and with gelatin. It is completely precipitated by lead acetate, and this property furnishes a means for its quantitative estimation. It is also removed from its aqueous solution by hide powder and by this means can be separated from citric or tartaric acids.

Tannic acid is used for the same purposes as gallic acid and is valuable in chronic diarrhea and as an antidote in alkaloidal poisoning. It is used

to a considerable extent in pile remedies, where it is combined with opium, camphor, menthol, boric acid, etc. Combined with glycerin it forms an efficient gargle for sore throat. Iodotannic acid used in gonorrheal injections consists of an alcoholic solution of tannic acid and iodin.

The commercial acid is often impure, containing varying amounts of foreign or transformation products insoluble in water.

In order to determine tannic or gallic acids a procedure based on that recommended by the writer for tea may be advantageously employed. Lead tannates contain definite quantities of lead, and if a solution containing the acid is precipitated by a known quantity of lead acetate in excess, and the lead remaining in solution determined, it is a simple matter to arrive at the amount of tannic acid. To carry out this procedure properly one must know the lead content of the tannate yielded by the drug in question, and this will naturally require a certain amount of research, for it will first be necessary to prepare the tannin in the pure condition. In the case of tea tannin the lead content is 48.3 per cent.

The following method will enable one to obtain a very accurate estimation of the quantity of tannic acid in tea:

Ten grams of powdered tea are transferred to an Erlenmeyer of 100-mils capacity, 50 mils petroleum ether added, stoppered, and shaken occasionally and allowed to stand overnight. It is then filtered through a dry filter and the flask and filter washed with petroleum ether until the filtrate comes through colorless. The powder is dried, returned to the flask, treated with 50 mils of 50 per cent alcohol, shaken from time to time, and allowed to stand overnight. It is filtered into a 500-mil graduated flask and filter washed with three portions of hot 50 per cent alcohol. After cooling, an excess of 10 per cent lead acetate solution is added (usually 50 mils will be sufficient), the mixture well shaken, made up to mark with 50 per cent alcohol and thoroughly mixed. As soon as the precipitate has settled, leaving a clear supernatant liquid, 10-mil portions are pipetted, concentrated over the steam-bath to drive off the alcohol, treated with 1 to 2 mils of dilute sodium hydroxide, washed into a small beaker, and submitted to the action of hydrogen sulphide. As soon as the precipitation is complete, the lead sulphide is filtered into a tared Gooch, washed with water, and dried *in vacuo* over sulphuric acid.

At the same time, a blank is run, using the same quantity of lead acetate made up to 500 mils, the difference in the lead sulphide figures, of course, being a measure of the lead taken up by the tannin. In this compound the lead amounts to 48.3 per cent, and it is thus a simple matter to figure the percentage of tannin.

Tannic acids are widely distributed in the plant world, and reactions for them will be obtained in most mixtures containing vegetable constituents. The study of the different tannins occurring in the medicinal

plants has hardly commenced. Their presence in mixtures is best detected in the aqueous alkaline solution after the shaking-out process. The liquid should be evaporated until the ammonia is driven off, lead acetate added in excess, the precipitate filtered, washed, and decomposed in the presence of alcohol to which a trace of ammonia has been added. On filtering and evaporating the alcohol the tannate will be left as an ammonium salt, and will give the characteristic tannic acid reactions.

Tannalbin

Tannate of albumin is a compound of tannic acid and albumin.

It is a light-brown, odorless, and tasteless powder, containing about 50 per cent of tannic acid. It is practically insoluble in water or alcohol but slowly soluble in alkaline fluids, which split it up into its constituents.

It is employed as an astringent in diarrhea.

Tannigen

Diacetyl-tannin is tannyl acetate, $(CH_3CO)_2C_{14}H_8O_9$, the acetic acid ester of tannin.

It is a light-gray, almost odorless and tasteless powder, which undergoes no change when heated alone, even to 180° C., but softens when heated in water at 50° C. It is practically insoluble in cold water, scarcely soluble in hot water, but soluble in alcohol, and also in solutions of borax, sodium phosphate, sodium carbonate, lime, etc., being precipitated from these solutions by acids. It is rapidly saponified by boiling sodium or potassium hydroxide solutions, or gradually in the cold, into acetic and gallic acids, while ammonia produces acetic and tannic acids.

Its aqueous solutions produce with ferric salts a green color, instead of the blue-violet color characteristic of tannic acid. A slightly alkaline solution in sodium phospate exhibits all the characteristics of an astringent and precipitates albumin, but these properties are destroyed by borax or more alkali.

Protan—Tannin Nucleo-Proteid

Protan is said to be a chemical combination of casein with tannic acid containing about 50 per cent tannic acid.

When shaken with water and filtered, a colorless solution should be obtained, which should give not more than a faint trace of color with ferric chloride solution, showing absence of more than traces of free (uncombined) tannic acids.

The resistance of Protan to the action of the gastric juice may be shown by mixing 2 grams (dried at 100° C.) with 40 mils .2 per cent hydro-

chloric acid containing ten times the theoretical amount of 1:3000 pepsin necessary to digest the proteid present, warming to 40° C. for six hours, filtering off the residue, drying and weighing; 60 to 70 per cent of the amount taken may thus be recovered.

The tannin may best be determined by difference, the casein being determined by decomposing it by the Gunning method and estimating the nitrogen.

It is employed as an intestinal astringent in all forms of diarrhea.

Tannismuth

Bitannate of bismuth is the bismuth salt of tannic acid in which approximately one atom of bismuth is combined with two molecules of tannic acid having approximately the formula, $Bi(OH)(C_{14}H_9O_9)_2$, and containing between 17 and 21 per cent bismuth.

It is a light yellow powder with slightly astringent taste, insoluble in water, soluble in cold caustic alkalies, and in diluted hydrochloric acid.

Tannismuth is used in chronic intestinal catarrh.

Tannoform

Tanninformaldehyde or methylenditannin, $CH_2(C_{14}H_9O_9)_2$, is a condensation product of formaldehyde with gallotannic acid.

It forms a voluminous, reddish powder, odorless and tasteless. It is insoluble in water, but soluble in alkaline liquids and in alcohol. One one-hundredth gram of tannoform dissolved in 2 mils concentrated sulphuric acid forms a brown solution which on warming becomes green and later changes to blue. The green or blue solution, on addition of alcohol, assumes a brilliant blue color, which gradually changes to wine color, while on addition of dilute sodium hydroxide the color is pale green.

Tannopin

Hexamethylene-Tetramine-Tannin, or Tannon, $(C_{14}H_9O_9)_3(CH_2)_6N_4$, is a condensation product of tannin with hexamethylenamine.

It is a fine, fawn-colored, odorless and tasteless, non-hygroscopic powder, containing 87 per cent of tannin and 13 per cent of hexamethylenamine. It is insoluble in water, weak acids, alcohol, chloroform, or ether, but slowly soluble in dilute alkalies. On heating dry tannopin, it swells and gives off the odor of formaldehyde. The odor of formaldehyde is also developed on heating tannopin with dilute sulphuric or hydrochloric acid, while on boiling with sodium hydroxide solution it splits off ammonia. The clear aqueous filtrate from tannopin does not give a reaction with ferric chloride.

It is used in intestinal catarrh.

Tanosal

Tanosal, creosal, or creosote tannate, is obtained when birchwood creosote and tannic acid are heated with phosphorus oxychloride. It is a dark-brown powder with a creosote odor, soluble in water, alcohol, and glycerin, but insoluble in ether, and used as an astringent and antiseptic.

Bismuth oxyiodotannate or ibit is a product of uncertain composition, used as a substitute for iodoform.

Pankreon is obtained by the action of tannin on pancreatic substances. It is soluble in alkaline liquids but not in water or acids, and is used in some forms of intestinal dyspepsia, gastritis, and carcinoma.

Gorter found that the tannic acids ascribed to many plants are in reality chlorogenic acid, $C_{32}H_{38}O_{19}$. This body is a dibasic acid, crystallizing in white anhydrous needles, melting 206–207°, having an astringent and slightly acid taste. It is soluble in water, ethyl and isobutyl alcohol, and acetone, slightly soluble in ether and acetic ether, insoluble in chloroform and carbon tetrachloride. Lævograte $(\alpha)_D = -33°1$.

Alkalies in excess color it yellow. It can be determined by titration with alkali, the end-point being marked by a yellow color. With ferric chloride it gives a green color changing to blue and to violet, red on addition of sodium hydroxide. Warmed with sulphuric acid and manganese dioxide the odor of quinone is given off. It reduces silver nitrate on warming, but Fehling's solution only slightly. Exposed to the fumes of ammonia in the air its solutions are first yellow gradually become green.

In alcoholic solution it is precipitated yellow by alcoholic potash and by lead acetate. It gives well-defined crystalline salts with calcium, magnesium, zinc, lead, benzidine, and strychnin.

It exists in coffee as the double salt of caffein and potassium, colorless, crystalline prisms, becoming yellow at 150° and charring without melting at 225°. The caffein is not removed by chloroform in the dry state, but when water is present it is separated.

On boiling with potash it is hydrolyzed to caffeic and quinic acids,

$$C_{32}H_{38}O_{19}H_2O = 2C_9H_8O_4 + 2C_7H_{12}O_6.$$

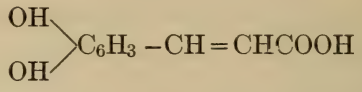
On acetylization a crystalline body is formed having 5 acetyl groups: $C_{16}H_{18}O_9(C_9H_3O)_5$. The group $C_{16}N_{18}O_9$ is called by Gorter hemichlorogenic acid, and is considered as proceeding from the decomposition of chlorogenic acid with the loss of one molecule of water.

$$C_{32}H_{38}O_{19} = H_2O + 2C_{16}H_{18}O_9.$$

In its turn hemichlorogenic acid is decomposed by alkalies or acids into one molecule of quinic and one molecule of caffeic acids.

Chlorogenic acid would then be formed from two molecules of quinic and two of caffeic acids without the least trace of carbohydrate.

Caffeic acid is 3–4 dioxycinnamic acid



It melts at 194–195°, gives a yellow color with ferric chloride, becoming reddish violet on adding sodium hydroxide. It is colored yellow by ammonia, reduces silver nitrate and gives a yellow precipitate with lead acetate.

Quinic acid is tetraoxyhexahydrobenzoic acid.

$$C_6H_7(OH)_4COOH$$

It melts at 161°, is lævogyrate, soluble in water, and gives a white precipitate with neutral lead acetate but none with basic.

Quinic acid has medicinal uses, being employed in uric acid diathesis in the form of salts, the most important being lithium quinate or urosin, piperazin quinate or sidonal, hexamethylenetetramine quinate or chinotropin, and urea quinate or urol.

For the detection of the acid in plants, the following color reaction is used:

Ten grams of leaves are boiled with 50 mils of dilute hydrochloric acid during one hour in a reflux apparatus. The filtrate from this is shaken with 15 mils of ether. The latter is washed with a dilute solution of sodium hydrogen carbonate and then twice with water, and to it is added a small quantity of a very dilute solution of ferric chloride, when, if chlorogenic acid is present in the leaves, a violet coloration is produced in the aqueous layer on shaking, while the ethereal layer develops a yellow tint. Out of 230 species of plants examined by Gorter in this way, 98 gave a positive result. The acid appears to occur in many plants of the orders *Acanthaceæ Araliaceæ*, *Convolvulaceæ*, *Boraginaceæ*, *Gesneraceæ*, and *Compositæ*.

Gorter's experiments also proved that the acid of Nux Vomica, formerly known as igasuric acid, was identical with chlorogenic acid.

VEGETABLE ACIDS USED MEDICINALLY

There are a few other acids occurring in drugs which are extracted in a more or less pure state and used for their medicinal properties. They are more conveniently considered under the discussion of the individual drugs, but attention will be called to them at this point.

Anacardic acid, from Anacardium occidentale (cashew nut), used as a vermifuge in the form of its ammonium salt.

Embelic acid, from the fruit of Embelia ribes, soluble in alcohol, ether, and choloroform, and used as a tape-worm expellant.

Filicic acid, from Malefern, used for the same purpose.

Caincic acid, from the root of Chiococca anguifuga or C. racemosa (Cainca root), soluble in alcohol and ether, and used in dropsy as a diuretic cathartic.

Quillaic acid, from the inner bark of Quillaja saponaria (soap bark), soluble in alcohol and water and used as an expectorant.

ARABIC ACID, $C_6H_{10}O_5+H_2O$

Arabic acid or arabin occurs in gum acacia, and may be obtained by dissolving the gum in water, adding hydrochloric acid and precipitating with alcohol. Its aqueous solution is acid in reaction and on evaporation leaves a vitreous mass which loses water above 120°, yielding metarbin. The latter does not dissolve but swells in water.

THE AROMATIC GUM-RESINS AND BALSAMS

The chemistry of the aromatic gum-resins and balsams is intimately connected with the chemistry of benzoic and cinnamic acids. The drugs themselves are complex mixtures, and no definite standards have been ascribed to them, in fact with the possible exception of gum benzoin it is doubtful if many of the analytical figures obtained and reported were obtained with pure products, collected under personal observation, and any data quoted must be taken with reservation.

The quantitative estimation of these drugs as a whole is really of little moment in comparison with the importance of estimating the amount of the potent ingredients in such products as Nux Vomica, aconite, etc. If a quantitative value is important, it may be confined to the determination of the aromatic acids in the free and combined condition, and as a matter of fact this is about all that can be accomplished with the pure drugs themselves, except where they are grossly adulterated and an approximate determination of the adulterant is desired.

The drug chemist often finds it necessary to pass upon the quality of a specimen of gum or resin, hence we will first discuss the properties and the composition of the individual drugs in the light of our present knowledge concerning them, and before proceeding with a detailed study of the composition, the worker should familiarize himself with the names and significance of the esters of benzoic and cinnamic acids which will figure largely in any work he will take up. These include:

Benzyl benzoate.

Benzyl cinnamate. Cinnamein.

Cinnamyl benzoate.

Cinnamyl cinnamate. Styracin.

The term " cinnamein " is applied not only to the ester benzyl cinnamate, but to the mixtures of esters, alcohols and other substances existing in the balsams of Peru and Tolu which are not extracted from an ethereal solution by alkalies. This point must be borne in mind constantly by the analyst, because its application may become a matter of importance in legal work.

Gum Benzoin

Gum benzoin, according to the Pharmacopœia, comes from the Styrax benzoin (Styraceæ) and probably other species of Styrax, but the researches of Holmes and those of Rordoff indicate that Siam benzoin comes from S. tonkinense. The trees producing it grow in the East Indies and Southern Asia and as far as can be determined different commercial grades of gum, Penang, Sumatra and Siam all come from the same plant.

Gum benzoin is the source of natural benzoic acid. Medicinally it is employed as a stimulant and expectorant in pectoral troubles and as a soothing lotion for wounds, fissures, bed sores, etc.

Traumatic balsam, Turlington's balsam or Friar's balsam consists of an alcoholic solution of benzoin, storax, Peru and Tolu balsams, aloes, myrrh, and angelica root, sometimes with licorice. Compound tincture of benzoin contains benzoin, aloes, storax, and Tolu.

Mixtures similar in composition to Friar's balsam have been known at different times as Jesuit's drops, Wade's balsam, baume de commandeur, etc. These " baumes " will often be encountered by those who work with imported preparations.

Benzoinated lard is prepared by incorporating fluid benzoin with pure lard or by digesting hot lard with powdered gum and then straining. This substance will often be found in salves and ointments mixed with various ingredients such as menthol, oil of mustard, Capsicum, etc.

Sumatra Benzoin

The drug occurs in irregular masses composed of yellowish or reddish-brown tears of variable size, and a reddish-brown and translucent or grayish-brown and opaque matrix; it is brittle and the tears are milky white internally. The drug becomes soft on warming and benzoic acid is yielded on sublimation; the odor is agreeable and balsamic, resembling that of storax, and the taste is aromatic. The mass often contains considerable quantities of imbedded bark.

Pelembang benzoin resembles the Sumatra, but is somewhat more transparent.

Penang benzoin resembles the Sumatra in appearance, but resembles the Siam more in composition.

Siam Benzoin

This drug occurs in concavo-convex white tears, often imbedded in a rich amber-colored translucent resin, with more or less admixed bark. The finer varieties are composed almost entirely of these tears loosely agglutinated together. It has a vanilla-like odor and a bitter taste.

Constituents of Sumatra Benzoin.—It is made up of about 75 per cent of a resinous substance, benzoresin, which consists of two esters, one an ester of cinnamic acid and resinotannol amounting to 90 per cent or more of the benzoresin, and the other an ester of cinnamic acid and benzoresinol. Benzoresin on saponification yields 30 per cent cinnamic acid, 65 per cent of resinotannol, and 5 per cent benzoresinol.

Sumatra benzoin also contains traces of benzaldehyde and benzol, .1 to 1 per cent of vanillin, 1 per cent phenypropyl cinnamate, 2 to 3 per cent of styracin (cinnamyl cinnamate) and 14 to 17 per cent of insoluble matter, mostly woody tissue.

Constituents of Siam Benzoin.—It is composed largely of a resinous substance, siabenzoresin, consisting of 90 per cent of an ester of benzoic acid and siaresinotannol, and about 10 per cent of an ester of benzoic acid and benzoresinol. Siabenzoresin on saponification yields 38 per cent benzoic acid, 57 per cent siaresinotannol, and 5 per cent of benzoresinol.

Siam benzoin also contains .3 per cent of a benzoic ester, .15 to 1.5 per cent vanillin, a small quantity of free benzoic acid and 1 to 4 per cent of woody impurities. Dieterich states that cinnamic acid takes part in the composition of Siam as well as of Sumatra benzoin. This gum usually commands from four to five times the price of the Sumatra gum.

Gum benzoin is produced under the stimulus of a wound in the tree, and cannot be a product of the bark. It is probably a pathological product of the injured protoplasm.

The common adulterants of benzoin are, besides excessive amounts of wood and bark, colophony, turpentine, storax, dammar, and other resins.

Reinitzer [1] states that Siamese benzoin first exudes as a milky white body and does not contain the brown siaresinotannol described by Ludy as its principal constituent. The benzoin in loose tears is crystalline, melting 59°, and on heating to 40 to 50° in the dark it becomes darker and amorphous, probably owing to an oxidation process. The purified crystals melt 72.8°, and consist of the benzoate of an alcohol which Reinitzer terms lubanol. They give a green color with ferric chloride, and are capable of combining with a further quantity of benzoic acid. They give the Liebermann-Salkowski reaction and a fine blue color on warming with chloral hydrate.

Siamese benzoin also contains the benzoate of a body resembling Ludy's benzoresitannol, but containing more oxygen. It melts at 279° C., crys-

[1] Ges. dent. Naturforacher und Aerzto, Sept., 1909; J. S. C. I., 1909, 1148.

tallizes in large prismatic needles, and is dextrorotatory in alcoholic solution. Reinitzer calls it siaresinol. It gives a sodium salt sparingly soluble in alcohol. It is not oxidized on heating to 50°, does not give a color with ferric chloride, but responds to the L–S reaction.

Siamese benzoin also contains an amorphous benzoate which turns reddish brown at ordinary temperatures and yields two bodies to carbon bisulphide. When heated at 100° in alkaline solution it is converted to Ludy's siaresinotannol.

Sumatra benzoin likewise exudes originally with a white color and the sumaresinotannol is a secondary oxidation product.

K. Dieterich has devised an examination applicable to benzoins in the commercial condition. This includes the estimation of ash and of data termed, respectively, " indirect acid number," " cold-saponification number," and " ester number." The last value is derived from the first two. The procedures are as follows: The weighed portions should be taken from a comparatively large amount of the material that has been finely powdered and well mixed.

Indirect Acid Number.—One gram is mixed in a flask with 10 mils of half-normal alcoholic alkali and 50 mils of 96 per cent alcohol. The mixture is allowed to stand exactly five minutes, and then titrated with half-normal sulphuric acid and phenolphthalein until the solution is yellow, and a fresh portion of the indicator does not turn red on being dropped into the liquid, and the sodium sulphate separates readily. The supernatant liquid must be yellow. The mils of alkali neutralized by the sample, multiplied by 28.08, gives the *acid number.*

Cold-saponification Number.—One gram of the sample is placed in a glass-stoppered flask with 20 mils of half-normal alcoholic alkali and 50 mils of light petroleum (sp. gr. .700). The flask, tightly closed, is allowed to stand for twenty-four hours at room temperature; after dilution with alcohol, the liquid is titrated with half-normal sulphuric acid and phenolphthalein. The mils of alkali neutralized, multiplied by 28.08, gives the cold-saponification number.

The ester number is the difference between the above data.

Dieterich gives the following as the limits of values with pure samples of the different benzoins:

	Siam	Sumatra	Palambang	Padang	Penang
	Per cent	Per cent	Per cent	Per cent	Per cent
Ash	0.03–1.5	0.0–1.5	1.1–4.02	1.07	0.38–0.77
Ind. A–N	140–170	100–130	113.4–130.9	121.8–124.6	121.8–137.2
Cold S–N	220–240	180–230	198–219.8	201.6–205.8	210–296.8
E–N	50–75	65–125	84–91	79.8–81.2	87.5–91.7
Sol. in 96 per cent alcohol	95	70–80	91		94

Balsams of Peru and Tolu

These drugs are so closely related chemically that both can be considered simultaneously.

The botanical source of Peru balsam has been the subject of some misunderstanding, and whether the species assigned to it has been confused with that of Tolu is a question for further study.

Peru is, according to the Pharmacopœia, a product of the Toluifera or Myroxilon periera (Leguminosæ). Kraemer describes the tree as growing to the height of 50 feet and having a short trunk with branches appearing about 6 to 10 feet from the base. The leaves are compound and with seven to eleven alternate oblong, acuminate, glandular, punctate leaflets; the flowers are white and in simple axillary racemes; the fruit is a winged indehiscent one-seeded legume. The balsam is collected by making incisions in the bark and collecting it in gourds. The plant is found over the whole of Northern South America, extending through Central America into Mexico, and is cultivated in Singapore.

A very fragrant vanilla-like balsam is obtained from the fruit of the same plant, and in San Salvador it is known as white Peru balsam to distinguish it from the dark product obtained from the trunk.

Dr. Albert Hale,[1] formerly of the Pan-American Union, has made a study of the interesting drug in its native heath, which he says is confined to a small area in the Republic of Salvador.

This Balsam coast extends along the western Pacific slope of Salvador, between the ports of Acajutla and La Libertad, a distance of only scant 40 miles, or allowing a short distance on either side the extreme limits of the recognized growth of the tree in all this region is only 50 miles. Assuming that this strip has a depth from the coast of 15 miles, which is very liberal indeed, there is an area of only 750 square miles at the most over which the tree is exploited. Why nature restricts her activities so curiously as in this instance is an interesting problem for the botanist.

The balsam tree is one of the most beautiful of a tropical forest. It may be found, in its natural state, in groups so evenly distributed as to suggest a plantation, but usually it grows rather isolated from its kind and even separated from its neighbors a respectful distance. In appearance it is a stout tree, measuring at full development about 1 meter (about 40 inches) in diameter and reaching upward as tall as 25 to 35 meters (80 to 115 feet). The trunk is cylindrical, the bark somewhat cracked, of a grayish or ashen color, with whitish blotches due to the parasitic lichen that cling to it. Few branches spring from it until the spread is reached, but the robust roots, especially in mature trees, extend along the surface

[1] Bull. Pan-Amer. Union, Vol. 22, 1911, 880.

of the ground before sinking finally beneath the soil. The bark of the branches and twigs is also gray or reddish and covered with numerous little white and hard excrescent-like spots. The outer wood is white, the inner is red or almost black, and extraordinarily hard; as it is also very durable it offers splendid material for construction work and furniture.

Flowering takes place through a stem of about 10 centimeters (4 inches) long, with numerous white blossoms. The fruit is a pale yellow, membranous, feathery pod, with only one seed, as a rule.

The life of the balsam tree is about one hundred years. The gathering of the sap is begun at the age of twenty-five years and may be continued indefinitely unless some accident to the tree occurs meanwhile.

A well-nourished balsam tree will yield on the average from 3 to 4 pounds of sap a year; the best of them, if cared for in anything like a modern agricultural system, can part with 8 pounds a year and still remain uninjured for the next seasom.

Only the inner bark yields pure balsam, and then only from the mature tree; although the immature tree does give juice, it is nevertheless thin, light, poor in quality, and of small commercial value.

This report from a man who has been on the ground certainly must be regarded in the light of authority.

Tolu comes from Toluifera or Myroxilon balsamum, a tree which, according to Kraemer, reaches the height of 75 to 80 feet and whose branches appear at a height of 50 to 60 feet. Otherwise its description is the same as T. pereira. It grows in Northern South America.

T. pernifera growing in Northeastern South America yields a balsam similar to Tolu.

It would seem as if Kraemer's description of the Tolu balsam tree more nearly corresponded with the tree which Hale found yielding Peru balsam.

Adulterants.—Peru balsam may contain Tolu balsam and storax, copaiba and gurjun balsams, turpentine, colophony, benzoin, castor oil. Owing to the rigid inspection during the last few years the grosser adulteration has ceased, but there exist in the market certain so-called " artificial " or " synthetic " Peru balsams, made from storax, Tolu and other substances with probably a little Peru.

Tolu balsam is relatively cheap and is not as liable to adulteration as is Peru. Colophony is the principal adulterant.

Peru is a warm stimulating stomachic and expectorant and emollient. It is used in chronic catarrh, asthma, phthisis, and pectoral complaints generally, and also in gonorrhea, leucorrhea, amenorrhea, chronic rheumatism, and palsy. Locally it is employed for ulcers, running sores, skin affections, and blood poisoning.

Combined with benzoin, tolu, etc., it is one of the constituents of Friar's balsam and other balsams and " baumes." It is dispensed in

syrups and with mucilage of acacia and mixed with lead plaster it is used as a remedy for blood poisoning, wounds, and other skin affections.

Tolu balsam has the same medicinal properties as Peru and will be found in the same class of compounds. Its greatest fame, however, is as a stimulant to the bronchial mucous membrane, and it occurs in the formulas of many mixtures recommended for coughs and colds.

Syrup of Tolu is official in the Pharmacopœia; liquid mixtures contain Tolu together with opium, ammonium chloride, licorice, wild cherry, and aromatics in syrupy form. Inhalants contain Tolu, iodin, phenol, glycerin, camphor, and cubebs.

Bronchial tablets are composed of Tolu with ammonium chloride, licorice, cubeb, Hyoscyamus, senega, and ipecac, sometimes with opium; and other formulas include Tolu with licorice, cubeb, and sassafras; with coltsfoot, licorice, peppermint, Capsicum, and anise. Throat pastiles are composed of mixtures of some or all of the following: Tolu, coltsfoot, licorice, sugar, acacia, horehound, wild cherry, anise, cubeb, and Capsicum.

Peru is a viscid balsam like syrup, honey, or molasses, of a dark reddish-brown color, a fragrant vanilla-like odor, and a warm bitterish taste, leaving when swallowed a burning or prickling sensation in the throat. It does not harden on exposure.

Tolu has at first a soft tenaceous consistency which varies considerably with the temperature. By age it becomes brittle and hard like rosin. It is shining, translucent, of a reddish or yellowish-brown color, a highly fragrant odor and a warm, somewhat sweetish and pungent, but not disagreeable taste.

Allen tersely summarizes these drugs as follows:

The cinnamic balsams are closely allied, consisting essentially of the benzyl and cinnamyl esters of benzoic and cinnamic acids, mixed with resinous oxidation products of these esters, free benzoic and cinnamic acids, and the hydrocarbon cinnamene. The leading or characteristic constituents of Peru balsam may be said to be the cinnamein or benzyl cinnamate and styracin or cinnamyl cinnamate. Free benzyl alcohol is also present. In Tolu balsam, on the other hand, the proportion of resin is large; but of the esters benzyl benzoate predominates, and cinnamyl benzoate and cinnamate exist in but small proportions. In liquid storax of Mexican origin, phenylpropyl cinnamate exists in considerable quantity together with two isomeric alcohol-like substances called α and β storesinol, to which the formula $C_{36}H_{55}(OH)_3$ is attributed, and the cinnamic esters of these substances.

In some cases the substances obtained from the cinnamic balsams have been decomposition products of the methods of analysis. The following method may be adopted for the recognition of the principal constituents of aromatic balsams: The substance is dissolved in 2 or 3

parts of ether, and filtered from any insoluble matter. The solution is agitated with an equal volume of normal sodium hydroxide, the alkaline liquid withdrawn, and the agitation repeated with a fresh quantity of solution. If desired, the total acidity of the balsam can be deduced from the titration of an aliquot part of the alkaline liquid. The ethereal layer is then washed with water, and distilled at a gentle heat, the residue of neutral ester, etc., being weighed. The residue is then fractionally distilled.

The first fraction will contain any *cinnamene* which may be present, the next being rich in *benzyl alcohol*, which may be extracted by agitation with water and will yield benzaldehyde and benzoic acid by oxidation. *Cinnamyl alcohol* and *benzyl benzoate* pass over next, and at the higher temperature *benzyl cinnamate* and *cinnamyl benzoate* and *cinnamate* may be obtained. These esters suffer more or less decomposition unless the distillation is conducted *in vacuo*, and hence the last fraction consists largely of cinnamic acid, which can be removed by agitating the distillate with sodium carbonate solution. The alkaline liquid separated from the ethereal solution should be saturated with carbon dioxide, which precipitates much *resin*. The liquid is filtered, concentrated, and treated with hydrochloric acid, when a bulky precipitate is obtained representing the *free benzoic* and *cinnamic acids* of the balsam. These substances may be identified by their ordinary reactions. For their approximate separation, one-half of the precipitate may be boiled with milk of lime and the liquid filtered and allowed to become cold, when the sparingly soluble calcium cinnamate is deposited in shining needles, the more soluble benzoate remaining in solution. When an exact estimation of the free acids of a balsam is desired, it is better to agitate the ethereal solution with sodium carbonate instead of sodium hydroxide, as the latter reagent is liable to cause some decomposition of the esters.

Methods for the Examination of the Peru and Tolu.—*Direct Acid Number.*—One gram of the sample is dissolved in 200 mils of alcohol (96 per cent) and titrated with decinormal alcoholic alkali, using phenolphthalein. The mils of alkali required multiplied by 5.616 gives the direct acid number.

Cold Saponification Number.—The procedure is mainly as given under "Benzoin," using 1 gram of the sample in a 500-mil glass-stoppered flask with 50 mils of light petroleum (sp. gr. .700) and 50 mils N/2 alcoholic alkali. After standing twenty-four hours at room temperature, 300 mils of water is added, well shaken, until the separated dark alkali salt has been dissolved, and the solution titrated, with continuous agitation, with N/2 sulphuric acid in the presence of phenolphthalein. The mils of alkali neutralized by the sample, multiplied by 28.08, gives the cold saponification number.

The *ester number* is obtained by subtracting the direct acid number from the cold saponification number.

Ether Insoluble Matter.—This is obtained by Dieterich by adding warm ether in small portions to a weighed portion of the sample until a portion of the solvent no longer leaves any residue on evaporation. The undissolved portion is then weighed. It will probably be better to extract in a Soxhlet tube.

Aromatic and Volatile Ingredients.—The ethereal extract is shaken with 20 mils of a 2 per cent sodium hydroxide solution, separated and evaporated at room temperature until no odor of ether is perceptible. The residue is placed for twelve hours in the desiccator, weighed, placed for a second twelve hours in the same and weighed again. The mean between these two weights is taken as the datum for fixed matter from which the volatile matter can be calculated.

Esters of Resin-acids.—The alkaline solution separated from ether by the action of the alkali, as noted in the last paragraph, is rendered acid by dilute hydrochloric acid, filtered through a tared filter and washed by the aid of a filter pump with as little water as possible until the washings are free from chlorides. The residue dried at 80° to constant weight is taken.

With these processes, Dieterich obtained from commercial samples of Peru Balsam the following range of data:

Sp. gr.	1.135	1.145
Direct acid number	60.0	80.0
Cold saponification number	240.0	270.0
Ester number	180.0	200.0
Resin esters	20.0%	28.0%
Aromatic and volatile ingredients	60.0%	77.0%
Ether insoluble	1.5%	4.5%

From authentic pure specimens from Honduras the following figures were obtained.

	I	*II*	*III*
Direct acid number	77.4	76.9	77.3
Cold saponification number	241.0	214.3	215.0
Ester number	165.6	137.4	137.6
Resin esters	15.7%	13.2%	17.3%
Aromatic and volatile ingredients	71.4%	77.5%	73.6%
Ether insoluble	4.4%	4.3%	3.5%

The United States Pharmacopœia requires that Peru balsam shall have a sp. gr. between 1.130 and 1.160 at 25°, that when mixed with sodium hydroxide solution, one extraction with ether shall remove 50 to 56 per cent of cinnamein, and that the latter shall have a saponification value of from 235 to 238. According to the same authority, Peru balsam must

have an acid value not less than 50 nor more than 84. The German Pharmacopœia regulation is satisfied if the 56 per cent of cinnamein is obtained by three successive extractions with ether, but it must require at least 23.66 per cent of potassium hydroxide for hydrolysis, and the balsam must have a cold saponification value not less than 224.6.

The acid number of Tolu balsam according to the U. S. P. should be not less than 112 nor more than 168, and the saponification value not less than 154 nor more than 220.

The U. S. P. method for determining these figures is as follows:

Dissolve about 1 gram of the Balsam, accurately weighed, in 50 mils of alcohol, add 1 mil of phenolphthalein T. S. and titrate the solution with half-normal alcoholic potassium hydroxide V. S. The acid number thus obtained is not less than 112 nor more than 168. Now add sufficient half-normal alcoholic potassium hydroxide V. S. to the neutralized liquid to make the total amount of the volumetric alkali solution exactly 20 mils; heat the liquid on a water-bath for half an hour, under a reflux condenser, and allow it to cool. Mix this liquid with 200 mils of distilled water, or more if necessary, and titrate the excess of potassium hydroxide with N/.5 sulphuric acid V. S.; the total amount of N/.5 potassium hydroxide V. S. consumed corresponds to a saponification value of not less than 154 nor more than 220.

The detection of rosin in Peru balsam may be effected by dissolving the balsam in ether and shaking the solution with sodium hydroxide which will dissolve out the acid constituents of the resin including any abietic acid. The alkaline liquid is then drawn off into another separator, acidified, and shaken with ether, the ether evaporated and the residue of mixed acids washed several times with boiling water to remove the cinnamic and benzoic acids, and then subjected to the test for abietic acid. This acid dissolves in chloroform and on adding a drop or two of acetic anhydride followed by a drop of concentrated sulphuric acid a purple color changing to blue is obtained.

Perrot and Goris detect rosin in Tolu by shaking 5 grams with 30 mils of carbon bisulphide in the cold or with gentle warming. The solvent is decanted and evaporated, the residue treated with 10 mils of light petroleum ether, filtered and shaken with a 1–1000 solution of copper acetate. The presence of rosin is indicated by the appearance of a green color. The authors state the reaction is not applicable to Peru balsam as the pure drug gives a green color. This assertion may be correct, but it is also possible that at the time the researches were in progress the Peru balsams all contained rosin.

Hartwich and Jama [1] from a study of the situation conclude that the balsams all come from the same tree, but of distant botanical varieties:

[1] Schweiz. woch. Chem., Pharm. 1909, 47, 625 and 641; J. S. C. I., 1901,1271.

Tolu from Myroxylon balsamum (L) var α-genuinum (Baill).
Peru from Myroxylon balsamum var β perierae (Baill).
Quino-quino Myroxylon balsamum var J. punctatum (Baill).
They tabulate the analysis of these bodies as follows:

Saponification No.	Cinnamein	Saponification No. of Cinnamein
257.4	65	236
255.5	65.5	243.5
261.3	65.9	243.6
263.7	62.4	262
265	61	264
255.3	60.8	265
272.1	57	271
269.3	60	265

A sample labeled " synthetic " gave:
Saponification No. 263.7, cinnamein 62.5 per cent, saponification No. of cinnamein 244.

Heiduschka and Rheinberger [1] record the results of some observations made with a bromination test upon Peru balsam containing various admixtures. A flask is fitted with a two-hole cork containing a pipette graduated to hold 1 mil of bromin and a thermometer; 20 mils of the solution of 10 grams balsam in 100 mils chloroform are introduced into a flask and when the thermometer has attained the temperature of the mixture the bromin is added and the temperature noted after $1\frac{1}{2}$ minutes. The pure balsam showed a value of 17°.

Drug	Bromin value with 5 per cent admixture. Degrees	Bromin value with 10 per cent admixture. Degrees
Tolu	17	17
Castor Oil	17.75	18.25
Storax	17.85	19
Copaiba	18.00	18.75
Turpentine	18.75	21.50
Venice Turpentine	18.75	20.50
Resin	19.00	20.00
Santal Oil	19.50	21.75
Gurjun Balsam	19.75	22.75
Benzoin	——	18.25

Jensen [2] records that cinnamein from reliable Peru showed iodin numbers of 23.8 and 25.5 against 1.5 from synthetic esters. Upon frac-

[1] Pharm. Centrh., 50, 220. [2] Pharm. J., 90, 210.

tional distillation of cinnamein the first 30 per cent was optically active when derived from the true balsam, but inactive when derived from the synthetic. Benzylbenzoate boils approximately 320° (ordinary pressure), 173° at 9 mm., sp. gr. 1.121, saponification number 264.1. Benzyl cinnamate boils 360° approx. (ordinary pressure), 213–214° at 9 mm., sp. gr. 1.098, saponification No. 235.3.

Merck's Method of Determination of Acid and Saponification Value.— One gram balsam is dissolved in 50 mils alcohol, 6 mils N/2 potassium hydroxide added, a few drops of phenolphthalein and after shaking, 200–300 mils water; the excess of alkali is titrated with N/2 hydrochloric acid and the volume of alkali used up by the balsam ×28 gives the acid value.

The saponification value is determined by dissolving 1 gram balsam in 50 mils alcohol, adding 20 mils N/2 alcoholic potash, heating one-half hour over the steam-bath, adding 200 to 300 mils water and titrating with N/2 hydrochloric acid. The volume of alkali consumed by the saponification ×28 gives the saponification value.

A method for determining " cinnamein " in aromatic balsams has been described by Lehmann and Muller.[1] A mixture of 2.5 grams of the balsam and 5 mils water is shaken for one minute with 30 mils ether in a 75-mil separator, 5 mils sodium hydroxide solution are added, shaken one minute and allowed to stand ten minutes; the aqueous solution run off until about 3 mils are left. After the addition of .5 gram tragacanth, the separator is shaken for three to five minutes and the ether poured off or filtered into a tared flask, evaporated and weighed.

Delpin's [2] method of testing balsams in order to differentiate between the acid and resin esters is as follows:

Balsam is dissolved in ether and shaken with N/1 sodium hydroxide, followed by 10 mils water. The ether is then evaporated and residue weighed as cinnamein. The alkaline solution is treated with 2 grams sodium bicarbonate and a stream of carbon dioxide slowly driven through the mixture for an hour, the solution filtered through a tared Gooch and the precipitate washed with warm water until the washings are no longer alkaline, the filtrate and washings being reserved. The precipitate on the Gooch is dried and weighed as resin ester. The alkaline solution is then treated with excess of hydrochloric acid, and the precipitated acids collected on a tared Gooch, washed with boiling water, dried and weighed as resin acids. The acid filtrate and washings are then shaken out with ether, and the cinnamic acid determined gravimetrically by drying *in vacuo* or by titrating in alcoholic solution.

[1] Arch. Pharm., 1912, 250, 1.
[2] Svensk. Farm. Tidshr., 1907, 3, 415.

Honduras Balsam

Tschirch and Werdmuller,[1] from an examination of three samples of light balsam, report specific gravity 1.0886, 1.0905, 1.0884, average acid value 32.67, average saponification value 173.2, corresponding to a total amount of 45.66 per cent cinnamic acid and 8.6 per cent free acid. Its odor resembles storax. When shaken with sodium carbonate it yielded cinnamic acid and a resin ester which yielded cinnamic acid and honduroresinol, melting 166–167°. On boiling with strong potassium hydroxide a phytosterol-like substance separated on cooling. The alkaline solution also yielded an amorphous substance called β-honduroresin, melting 300°, insoluble in hot alcoholic potash, alcohol, ether, acetone, or petroleum ether with no phytosterol reactions. The " cinnamein " remaining after extracting the ether solution with alkali is a mixture of a hydrocarbon, C_8H_{10}, hondurane, boiling 154–155°, distyrene; another hydrocarbon, C_9H_{12}, boiling 140–155°; cinnamyl and phenyl-propyl cinnamates, and hondurol, $C_{17}H_{16}O_2$, a dihydric unsaturated alcohol, melting 42.5°.

Two dark samples gave an average acid value 29.9 and saponification value 153.9. They yielded products similar to the above.

Tschirch and Werdmuller [2] have investigated Cabureiba balsam from Myrocarpus fastigiatus and M. frondosus from Peru, an aromatic balsam. It contains benzoic acid, vanillin, and a new resinotannol, but no cinnamic acid nor cinnamein.

Patents have been obtained for soluble preparations of Peru balsam obtained by mixing the ingredients in the following proportions: 100 grams balsam with 50 grams glycerin, 50 grams 90 per cent alcohol and 50 mils potassium hydroxide solution 43° B., heating for several hours at 60° C. and running in gaseous formaldehyde, the process being continued until the product forms a clear solution with water.

Storax

Storax, styrax, or Oriental sweet gum, is obtained from the plant Liquidambar orientalis (Hamamelidaceæ). The tree grows profusely in the forests of Asia Minor, it is from 20 to 40 feet high. The leaves are palmate, the divisions obscurely three-lobed, serrate, smooth, bright green on upper and pale on under sufrace.

Other species of Liquidambar yield a similar, if not an identical gum; L. styraciflua, the sweet-gum tree of this country exudes a storax used to some extent commercially and the resins from L. formosana and L. altingiana are of commercial importance. Storax is also obtained from the trees of the closely related genus Altingia.

[1] Arch. Pharm., 248, 420.

[2] Arch. Pharm. 248, 431.

At the present time our Pharmacopœia recognizes only the resin of L. orientalis.

It may be found adulterated with turpentine, colophony, castor or olive oils, labdanum, and cheap resins.

It is used for the same purposes as Peru and Tolu balsams and may be found in the same class of formulas.

Storax furnishes the aromatic component of some of the imitation Peru balsams.

An extract of the bark of L. styraciflua furnishes a mucilaginous astringent which has been used in diarrhea and dysentery.

Storax is a viscid, grayish, more or less opaque semiliquid mass, depositing on standing a heavier dark brown, oleoresinous stratum; translucent in thin layers; odor agreeable, taste balsamic.

It consists of about 50 per cent of two resin alcohols, α-storesin, and β-storesin, which are partly free, partly in combination with cinnamic acid and partly with sodium. α-storesin (α-storesinol) is an amorphous substance that is very sparingly soluble in water and forms a crystalline compound with potassium.

β-storesin (β-storesinol) occurs in white flakes somewhat soluble in water, and not forming a crystalline compound with potassium. Storax also contains from 10 to 20 per cent of an ester consisting of cinnamic acid and storesin; from 5 to 10 per cent of cinnamyl cinnamate; 10 per cent of phenylpropyl cinnamate, odorless and viscid; 2 to 3 per cent of phenylethylene (styrene) which occurs as a colorless liquid possessing the odor and pungent taste of the drug; from .5 to 1 per cent of a lævorotatory volatile oil; 2 to 5 per cent of free cinnamic acid; about .15 per cent vanillin, and small quantities of benzoic acid, ethyl vanillin, resin, caoutchouc, and undetermined substances. It sometimes yields more than 20 per cent of free cinnamic acid.

Burmese storax from Altingia excelsa is a soft white crystalline balsam developing the fragrant odor of styrene, and contains about 50 per cent of cinnamic esters. A brown solid balsam is also obtained from the same tree having a cinnamein-like odor, and containing a trace of free cinnamic acid and about 10 per cent of cinnamic esters.

The examination of storax should in general follow the lines indicated under the other balsams and the same directions may be followed.

Tschirch and van Itallie [1] have examined storax from L. orientalis and find free cinnamic acid, vanillin, stryol, styracin, ethyl cinnamate, and storesinol partly free and partly as ester. No benzoic acid was detected. Storesinol is a white, odorless powder, melting 156–161°, $C_{16}H_{26}O_2$, insoluble in light petroleum ether, but dissolves in other organic solvents and in alkalies. It is isomeric with benzoresinols but with a

[1] Arch. Pharm., 239, 506.

lower melting-point. It forms crystalline compounds with potassium hydroxide, separating in acicular crystals. It yields acetic and salicylic acid on alkaline fusion. On distillation with zinc dust it yields, phenol, toluene, and benzene. It does not acetylate nor give a benzoyl compound, nor any derivative with hydroxylamin nor phenyl hydrazine. Oxidized with nitric acid it gave picric and oxalic acids.

The same authors [1] working on American storax say that the constitutents are much the same, consisting of cinnamic acid, vanillin, styrol, styracin, cinnamic phenyl propyl ether, and styresinol partly free and partly in form of cinnamic ester. No ethyl cinnamate was detected. Styresinol is apparently an isomeride of storesinol having the same formula and melting-point but differing in optical activity, its specific rotation being $+13^\circ$ 19′ as compared with $+52^\circ$ for storesinol. In all other respects the resins are identical.

Determination of Total Cinnamic Acid.—The sample is saponified with excess of alcoholic potash, the alcohol evaporated, the residue dissolved in water, transferred to a separator, washed with 10 mils ether and the ether rejected. An excess of dilute sulphuric acid is added and the liberated acids shaken out with 3 portions of ether. The ether is collected in a flask, evaporated, and the residue boiled with 50–100 mils of water under a reflux; the water filtered off while hot into another separator; and the extraction with boiling water repeated twice. The combined aqueous solutions when cool are then shaken out three times with ether, the solvent filtered and evaporated and the residue dried *in vacuo* or titrated.

Umney records the analyses of samples of storax imported from 1907–1911 in which the acid values rose from 68 to 111, the ester values fell from 112 to as low as 14 in individual cases, but averaged in the last 60–70, and the cinnamic acid free and combined fell from 19 per cent to 2.5 per cent. He also worked on two samples which Professor Greenish had kept for eleven years, the crude resin showing acid values 50.6, ester value 100.4, total cinnamic acid 20.6 per cent. This sample yielded a purified storax with acid value 60.1, ester value 130.1 and total cinnamic acid 25.5 per cent.

Purified storax is prepared by dissolving the resin in alcohol, separating from the insoluble portion and removing the solvent. It is a brownish-yellow viscous balsam, transparent in thin layers, with an agreeable odor and balsamic taste, entirely soluble in alcohol and ether. When heated on a water-bath it should lose not more than 5 per cent. The acid value should range between 60 to 90 and the ester value 110 to 140.

Storax adulterated with rosin yields to petroleum ether from 55 to 65 per cent, the extract having an acid value 116 to 121, and saponifica-

[1] Arch. Pharm., 239, 532.

tion value (cold) 171 to 177. Pure storax gives a 37 to 47 per cent extract with acid value 37 to 47 and saponification value (cold) 194 to 198.

Nan-ta-yok or Burmese Storax

Hooper [1] examined this balsam, which has long been used in Burma as incense and for medicinal purposes. It is produced by Altingia excelsa (Noronha), a large tree (150 to 180 feet high) growing in the forests of the Indian Archipelago, Burma, Assam, and Bhutoa, and especially in the Tenasserim province of Burma. It is also found in China, Java, Cochin China, New Guinea, and Sunda Archipelago. Three samples of resinous balsam from Java examined by Tschich and van Itallie were said to be the products of two species of Altingia, but in Greshoff's opinion both trees were Altingia excelsa. The two aromatic exudations from South Tenasserim examined by the author had the following properties:

Soft White Crystalline Balsam.—This resembles honey when fresh, but after two years crystallized, and become white, and had a fragrant odor of styrol. It melted at 41° C., and when heated on the water-bath lost 7.65 per cent in weight, the volatile substances being chiefly essential oils. It gives the following values: Acid value, 24.96; saponification value, 199.35; and iodin value, 57.3. About half the balsam consisted of an ester of cinnamic acid, the amount of the latter separated being 37 per cent calculated on the original balsam.

Dark-brown Solid Balsam.—This consisted of resinous masses which yielded brown powder with an aromatic odor in which that of cinnamon predominated. After clarification with alcohol two samples gave the following results: Resins, 53.72 and 54.70; organic impurities 19.09 and 28.05; inorganic impurities 22.24 and 10.67; and volatile oil and loss, 4.95 and 6.58 per cent. The purified resin (m. pt. 68° C.) was clear, gave amber color, and had the fragrant odor of the crude balsam. It was soluble in chloroform, carbon bisulphide, and benzene, partially soluble in acetic ether, and slightly soluble in petroleum spirit.

	Acid Value	Saponification Value	Iodine Value
Crude Resins.....	52.48	130.10	41.07
Pure Resins.....	76.80	130.44	51.68

The brown balsam contained a trace of free cinnamic acid, and 9.7 per cent of that acid in the form of an ester. The author's conclusion is that the white balsam is valuable as a perfume and as a source of cinnamic

[1] Agri. Ledger, 1904, 115.

acid, while the brown balsam is of value as a perfume and as incense. Both possess a sweeter aroma than genuine storax, and when heated with sulphuric acid and potassium bichromate, both evolve an odor of benzaldehyde. If examined by Dieterich's method the brown resinous balsam cannot be regarded as true storax, while the white balsam only agrees with that resin in the saponification value. Hence the author's results confirm the statement of Tschirch and van Itallie that Nan-ta-yok resin differs in constitution from the genuine storax of Asia Minor.

SULPHONIC ACIDS AND THEIR DERIVATIVES

Sulphanilic acid, $C_6H_4(NH_2)SO_3H$

This acid, which is chemically amidobenzene-*p*-sulphonic acid, is prepared by heating anilin sulphate to 200° C. It crystallizes with $2H_2O$, readily soluble in hot, but sparingly in cold water, and insoluble in alcohol and ether; on heating to 280–300° it is decomposed. It forms salts with bases, but does not combine with acids, the basic character of the amido group being neutralized by the acid character of the sulphonic; when fused with alkali it yields anilin. Chromic acid oxidizes it to quinone. When dissolved in dilute sodium hydroxide and mixed with a slight excess of sodium nitrite, and poured into cold dilute sulphuric acid, diazobenzene sulphonic acid is formed.

$$C_6H_4\begin{cases}NH_2\\SO_3H\end{cases} + HONO = C_6H_4\begin{cases}N:NOH\\SO_3H\end{cases} + H_2O,$$

which compound immediately loses water and separates as the anhydride in colorless $C_6H_4\begin{cases}N:N\\SO_3\end{cases}>$.

In medicine sulphanilic acid is used in Ehrlich's diazo reaction for typhoid urines, and is sometimes given for chronic catarrh.

Cosaprin, Sodium acid sulphanilate, $C_6H_4\begin{cases}SO_3Na\\NH(COCH3)\end{cases}$ is used as an antipyretic.

PHENOL SULPHONIC ACIDS

Phenol-*o*-sulphonic acid, $C_6H_4OHSO_3H$, is formed, together with a small quantity of the *p*-acid when a solution of phenol in concentrated sulphuric acid is kept for some time at ordinary temperatures. It has been stated that on heating to 100–120° the *o*-acid is gradually converted to the *p*-acid, but recent experiments indicate that this is erroneous.

The *o*-acid known as ortho-sulphocarbolic or sozolic acid, is soluble in water, glycerin, and alcohol, but not in ether. It has a phenol-like odor and gives a violet color with ferric chloride. It is used extensively as an antiseptic. Aseptol, which is sold as a 33 per cent solution of the *o*-acid, really consists in large parts of the *p*-acid.

Phenol-*p*-sulphonic acid is a powerful antiseptic and its sodium and zinc salts are official in the Pharmacopœia. Solutions of this acid coagulate albumin, and give a violet color with ferric chloride, but the phenol sulphonic acids are readily distinguished from salicylic acid as they are not removed from acid solution by ether or chloroform. On boiling a solution of the acid with an equal volume of concentrated nitric acid and neutralizing with potassium hydroxide, a yellow color due to picrate is produced. On adding bromin to a solution of the acid a precipitate of tribrom phenol is thrown down, and sulphuric acid is liberated in solution, recognizable by its insoluble barium precipitate. The acid, on heating to 250° with potash, gives resorcinol. The potassium salt on fusion with potash yields catechol.

When the sodium salt is ignited it leaves in part a residue of sodium sulphate. The zinc salt does not yield the sulphate unless sodium carbonate is present.

The aluminum salt is known as Sozal. It is soluble in water and used as a substitute for iodoform.

Mercury phenol parasulphonate also called Hydrargyrol, is soluble in water and glycerin and insoluble in absolute alcohol. It is used as an antiseptic in place of mercuric chloride.

The estimation of the acid may be accomplished by the nitric acid reaction, precipitating the sulphuric acid formed, by means of barium, and weighing the barium sulphate, or it may be done by the following bromin method: .2 to .3 gram of the acid or salt with .6 to 1 gram barium chloride are dissolved in 100 mils water containing 10 mils hydrochloric acid 1.19 sp. gr. The mixture is heated to 60 to 65° and slowly treated with a solution containing, 1 gram potassium bromate and 5 grams bromide in 100 mils, until a faint persistent yellow color is produced. A small quantity of an alcoholic solution of phenol is added to remove the excess of bromin and then sufficient alcohol to dissolve the tribrom phenol. The container is then boiled and the liquid decanted from the barium sulphate, which is repeatedly washed with 50 per cent alcohol, then with water and finally filtered and weighed.

Nitroparaphenol sulphonic acid in the form of a soluble salt with potassium and mercury known as Phenegol is a reddish-brown, odorless, tasteless powder, soluble in water and used as an antiseptic. Its composition is given as $C_6H_5(ONO_2SO_3K) : Hg : (KSO_3NO_2O)C_6H_5$.

Analogous to the phenolsulphonic acids are resorcinoldisulphonic acid,

$C_6H_2(OH)_2(SO_3H)_2$, and thymol sulphonic acid, $C_{10}H_{12}OHSO_3H$, both soluble in water and alcohol, the former decomposing above 100° and the latter melting at 91–92°.

Diiodoparaphenol sulphonic, soziodolic acid or soziodol, $C_6H_2I_2(OH)SO_3H$, is a white crystalline powder, slightly soluble in cold water, readily in alcohol and glycerin, decomposed on heating to 200° with evolution of iodin. It gives a violet color with ferric chloride and a white precipitate with silver nitrate soluble in nitric acid. Its salts are used to some extent in medicine, especially those of mercury, sodium, potassium, zinc, and magnesium. They are antiseptic and antipyretic.

Ichthyol Compounds

On distilling certain bituminous shales an oily product known as crude ichthyol oil is obtained. This raw product on treatment with concentrated sulphuric acid yields a sulphonated product, probably a mixture of sulphonated hydrocarbons, and other sulphonated products with a variety of undertermined substances. On neutralizing the sulphonated acids with ammonia and evaporating to a thick syrup, the product known commercially as ichthyol or ammonium ichthyol sulphate is obtained. There are a number of other ichthyol compounds and they are all used for antiseptic purposes, owing their efficiency probably to the sulphonic bodies contained therein. They are recommended also as antiphlogistics, anodynes, and alteratives and are dispensed for internal and external use. They are often found in ointments, suppositories, and bougies, in remedies for ivy poisoning and in mixtures for uterine ailments combined with iodin, boric acid, Hydrastis, glycerin, and phenol.

There are a number of imitations of the natural product on the market, but whether they are any less effective than the genuine is still a matter for physiological research.

The sulphur in the product made from the natural distillate is present in three forms, first the combined sulphur naturally occurring in the distillate, second, the sulphur introduced by sulphonating and third, that in the form of sulphate.

Both of the ammonium and sodium compounds are brown syrupy liquids with a bituminous odor and taste. Water or a mixture of alcohol and ether dissolves the liquid, and pure alcohol or ether takes it up in part. Hydrochloric acid precipitates a resinous mass which is soluble in ether. The ammonium compound gives off ammonia on warming with caustic alkalies. The compounds of lithium, zinc, mercury, and silver have been prepared and are used as drugs.

The reactions and tests for ichthyol (the ammonium compound) may be briefly stated as follows:

The aqueous solution (1:10) has a faintly acid reaction upon blue litmus paper, and yields a greenish-black, resin-like precipitate upon the addition of hydrochloric acid. This precipitate is partially soluble in ether and alcohol; soluble in water, but if dissolved in the latter solvent it may again be precipitated from solution by the addition of hydrochloric acid.

With barium chloride test solution it gives a brownish-black precipitate which is soluble in dilute hydrochloric acid.

Ichthyol is incompatible with acid and saline solutions, fixed alkalies, their carbonates and iodides, alkaloidal salts, and mercuric chloride.

If dried at 100° C. ichthyol should not lose more than 47 per cent of its weight.

If from 5 to 6 grams of ichthyol are weighed into a flask, 25 mils of potassium hydroxide test solution and 100 mils of water added, the mixture distilled until no more ammonia passes over, the distillate collected in 15 mils of normal sulphuric acid to which 1 drop of methyl red test solution has been added, and the excess of acid then titrated with N/10 potassium hydroxide, the amount of normal sulphuric acid consumed should correspond to from 2.9 to 3.4 per cent of total ammonia (NH_3).

If from 5 to 6 grams of ichthyol are weighed into a beaker, diluted with 50 mils of water, 10 mils of a 10 per cent solution of albumin added, followed by 5 portions of 5 mils each of diluted hydrochloric acid, shaking after each addition, the mixture made up to a volume of 500 mils and filtered through a dry filter, and if 200 mils of the filtrate are heated to boiling, 10 mils of barium chloride test solution added, the mixture allowed to stand for twenty-four hours, the precipitate of barium sulphate collected, heated and weighed in the usual way, the weight of barium sulphate obtained should correspond to from 5.7 to 6.2 per cent of ammonium sulphate.

If from .5 to 1 gram of ichthyol is weighed into a Kjeldahl flask, diluted with 30 mils of water, 5 grams of potassium chlorate added, followed by 30 mils of nitric acid, the mixture evaporated to about 5 mils, 25 mils of hydrochloric acid again added, this solution evaporated to about 5 mils 100 mils of water added, the solution heated to boiling, 10 mils of barium chloride rest solution added, the mixture allowed to stand for twenty-four hours, the precipitate of barium sulphate collected, heated, and weighed in the usual way, the weight of barium sulphate should correspond to at least 10 per cent of the total sulphur.

If the ammonia contained in the ammonium sulphate as previously determined in ichthyol is calculated, and the result subtracted from the " total ammonia " as previously determined, the remainder should represent the ammonia combined with the organic sulphonic acids. If this

value is multiplied by 1.88 the result should represent the sulphur present in the sulphonic acids in an oxidized state, i.e., the " sulphonic sulphur."

If the sulphur contained in the ammonium sulphate as previously determined in ichthyol is calculated, and the result subtracted from the " total sulphur " as previously determined, the remainder should represent the sulphur present in the organic-sulphonic acids contained in the substance.

If the " sulphonic " sulphur in icythyol as previously calculated is subtracted from the sulphur in the organic-sulphuric acids as previously calculated, the remainder should correspond to at least 5.5 per cent of " organic " (" sulphidic ") sulphur.

Calcium Ichthyol is a derivative of ichthyol in which calcium is substituted for ammonium.

It is a brown, tasteless powder, insoluble in water, and containing 2.5 per cent of calcium.

Ichthalbin.—Ichthyol Albuminate is a compound of ichthyol-sulphonic acid and albumin analogous to tannalbumin.

It is a extremely fine, grayish-white powder, odorless and practically tasteless, insoluble in water, in the gastric juice, or in acid liquids, but completely soluble in alkaline liquids.

Ferrichthyol is a brown-black permanent powder, nearly odorless and tasteless, containing 2.5 per cent iron. It is insoluble in the ordinary solvents, acids or alkalies.

Tumenol

Tumenol is a mixture of sulphones and sulphonic acids obtained from bituminous minerals and in the crude form is a blackish-brown liquid soluble in ether.

Tumenolsulphone is that portion of the crude mixture which is extracted by ether after saponification. It is used in antiseptic ointments.

The acid products obtained from the crude oil are solid and easily soluble in water.

These materials are all used as antiseptics in skin diseases.

BILE ACIDS

Oxgall or bile both in its original condition and in a purified state is recognized by the U. S. Pharmacopœia, and as a remedy is employed in gallstones, constipation, catarrhal jaundice, and other conditions of a diseased liver. The purified bile of the hog and other animals is also used medicinally. It is probable that the efficiency of these secretions

is due, at least in part, to the animal acids which they contain. These acids have been separated in a condition of greater or less purity and sold under various proprietary names for diseased conditions.

Inspissated oxgall is prepared by straining fresh bile and evaporating to the consistency of a solid extract.

Oxgall is combined with other chemicals in various mixtures intended as tonics for convalescents and for anæmics and consumptives. It will be found in admixture with hypophosphites in liquid preparations, with modified or so-called "metabolized" oils and with extracts of other animal secretions, spleen, testicles, etc.

The purified bile is dispensed alone in pill, tablet, and capsule form. Some of the combinations include ginger, colocynth, pancreatin, pepsin, Nux Vomica; also shotgun prescriptions of some or all of them together and with perhaps the further addition of aloes, berberin, stramonium, quinin, and Taraxacum.

Comparatively recent investigations have elucidated the composition of bile and demonstrated the presence of complex nitrogenous and nitrogenous sulphur acids. Some of these acids have been separated in a fair condition of purity, and a number of products have appeared on the market, the activity of which is credited to these acids. Glycocholic, $C_{26}H_{43}O_6N$, and taurocholic acids, $C_{25}H_{45}O_7NS$, occur in oxbile in the form of their sodium salts. They may be separated in the following manner. Dry oxbile is treated with absolute alcohol and the tincture precipitated by ether in excess. Both salts are deposited and the glycocholate crystallizes upon standing, the taurocholate remaining in amorphous form, resembling oily or resinous matter. If the deposit is dissolved in water, solution of lead acetate will throw down a lead glycocholate, while the addition of lead subacetate to the remainder will precipitate the taurocholate.

All the bile acids respond to Pettenkofer's test. A small portion of the salt is dissolved in a little concentrated sulphuric acid in a small porcelain dish and warmed, care being taken that the temperature does not rise higher than 60° to 70° C. A 10 per cent solution of cane sugar is then added drop by drop while the liquid is stirred with a glass rod. If compounds of cholic acid are present a beautiful red color will appear, which does not disappear at room temperature, but usually in the course of a day becomes bluish violet. The red liquid shows in the spectrum two absorption bands, one at F and the other between D and E near to E. Care must be taken not to heat too much nor to add too much sugar. The sulphuric acid must be free from sulphurous acid and the lower oxides of nitrogen. As albumin, oleic acid, amyl alcohol, morphin, etc., may give a similar reaction, spectroscopic examination should not be omitted in doubtful cases.

Furfurol Test (Mylius): The substance is dissolved in alcohol and for every mil of the alcoholic solution, one drop of a 1 : 1000 furfurol solution and one mil of concentrated sulphuric acid are added and the mixture cooled, if necessary, so that the temperature may not rise too high. The same color reaction occurs as in Pettenkoffer's test.

Both glycocholic and taurocholic acids generally undergo hydrolysis under the influence of dilute acids or alkalies. The former yields cholalic acid, $C_{24}H_{40}O_5$, and glycocoll, $C_2H_5O_2N$, and the latter cholalic acid and taurine, $C_2H_7O_3NS$.

Glycocholic acid, $C_{23}H_{39}O_3 \cdot CO \cdot NH \cdot CH_2COOH$, forms glistening scales or needles which vary in melting-point from 132–152°, depending on the mode of preparation. It is slightly soluble in hot water and ether, readily soluble in alcohol and insoluble in chloroform and benzole.

Taurocholic acid, $C_{22}H_{39}O_3CONH \cdot CH_2CH_2—SO_2OH$, forms hygroscopic silky needles, readily soluble in alcohol and water, insoluble in ether, benzol, and acetone. When heated, it contracts at 140° and begins to break up at 160°, forming a liquid at 180°. Its solution in water has the property of holding up glycocholic acid.

Both acids are dextrorotatory. The amount of taurocholic acid may be estimated by calculation from the amount of sulphur contained in an alcoholic solution of the bile.

Cholalic or cholic acid, $C_{20}H_{31}\begin{cases}\text{COOH}\\(\text{CH}\cdot\text{OH})_2\\\text{CHOH}\end{cases}$, crystallizes in the form of rhombic plates or prisms with one molecule of water, or from alcohol in rhombic tetra- or octahedra with one molecule of the solvent. The crystals are very sparingly soluble in water and ether, but dissolve readily in alcohol. The alcohol molecule may be driven off by heating between 100–120°, and the acid melts 195°. The acid gives a blue compound with iodin. When added to 25 per cent hydrochloric acid at the ordinary temperature, a violet-blue color gradually develops, changing slowly to green and yellow. The blue solution shows an absorption band at D.

Glycocholeic acid, $C_{27}H_{45}O_5N$, and taurocholeic, $C_{27}H_{47}O_6NS$, occur in bile. Hyoglycocholic acid, $C_{27}H_{43}O_5N$, is obtained from pig's bile. Cheno-taurocholic acid is the chief taurocholic acid of goose-bile. Hyocholic acid, $C_{25}H_{44}O_4$, and chenocholic acid, $C_{27}H_{44}O_4$, are obtained by the hydrolysis of the conjugated acids of the bile of the pig and goose respectively.

Oxbile itself may be described as a brownish or dark-green, somewhat viscid liquid having a peculiar unpleasant odor and a disagreeable bitter taste. It has a specific gravity of 1.015–1.025 at 25° and is neutral or faintly alkaline. A small quantity of an aqueous mixture when treated with a crystal of sugar which is allowed to dissolve and afterward with a

drop or two of sulphuric acid cautiously added until the precipitate first found is redissolved will give a brownish color changing to carmine, purple, and violet. Attention should be directed to this reaction because it simulates that given by cod-liver oil and sulphuric acid, and both cod-liver oil or cod-liver extracts are dispensed with oxgall.

Purified oxgall is virtually an alcoholic extract of bile. The albuminoids present in the original secretion are mostly absent, but the bile acids, pigments, etc., are still present. It is completely soluble in water and alcohol and the aqueous solution is not precipitated by alcohol.

The mixed salts of bile acids will be found on the market under various proprietary names.

Colalin

Colalin consists essentially of a mixture of hyoglycocholic and hyotaurocholic acids, obtained from bile. To preserve the pulverulent condition a little magnesium carbonate is added.

It is a yellow powder of faint odor and persistent bitter taste. It melts at 103 to 107° C., is slightly soluble in water, and acid toward litmus.

Colalin should be readily soluble in alcohol and this solution should rotate polarized light to the right. It should dissolve almost entirely in a dilute solution of sodium carbonate with evolution of carbon dioxide and in a dilute solution of sodium hydroxide. The solution in sodium hydroxide should not be rendered turbid by the addition of barium hydroxide (absence of fatty acids). It should not contain more than a trace of sulphur (absence of taurin).

This product which is usually sold in the form of tablets is recommended for the removal of gallstones.

NUCLEIN, NUCLEIC ACID, AND NUCLEATES

Nucleins are modified nucleoproteins obtained by peptic digestion or by treatment with dilute acids. They are split up by the action of alkalies or by tryptic digestion into a protein constituent and a nucleic acid varying somewhat with the source of the nucleoprotein from which they are derived. The nucleic acids of commerce are apt to contain some protein in combination. They are most commonly made from yeast cells, but have been made, also, from the wheat embryo, the sperm of certain fishes and from the thymus and pancreas glands. In composition they approximate the formula $C_{40}H_{52}N_{14}O_{25}P_4$. From the wheat embryo products with relatively more nitrogen have been obtained.

Nucleins are colorless, amorphous, insoluble in alcohol and ether and insoluble or slightly soluble in water. They are more or less readily dis-

solved by dilute alkalies. They give the biuret test and Millon's reaction. They show a great affinity for many dyes, taking them up from aqueous or alcoholic solutions. The term nuclein is sometimes used to designate an impure nucleic acid, which usage has led to confusion, as the nucleic acids are bodies of definite composition.

Both nucleins and nucleic acids yield metaphosphoric acid on incineration. On fusion with potassium nitrate and sodium carbonate they yield alkali phosphates.

Nuclein and nucleic acid and nucleates are said to increase the number of white corpuscles, and it has been claimed that this increases the resistance to infection.

Nuclein and nucleic acid and nucleates have been used in tuberculosis and various infections.

The crude nuclein is separated from the yeast by bringing into solution the albuminous substances and nuclein by means of an alkali, precipitating the albuminous substances by adding acetic acid and heating to 75°, filtering and precipitating the crude nuclein from the filtrate by acidulated alcohol. It is purified by dissolving in water or weak alkali, adding dilute potassium permanganate, filtering, and again precipitating with acidulated alcohol.

Another process consists in acting on yeast in presence of water at a temperature of 70–75° with sodium zincate, aluminate or similar metallate, acidifying with acetic acid, filtering, heating, and throwing out the sodium nuclein compound with alcohol. From this salt the nuclein is obtained by dissolving it in a little water and pouring into alcoholic hydrochloric acid solution.

Pure nucleic acid is a white amorphous powder with an acid reaction readily soluble in water containing a little alkali, insoluble in alcohol and ether. From its solutions in alkalies, it may be precipitated by hydrochloric acid, but not by acetic acid. When chemically pure it does not give the biuret test or Millon's reaction, but the commercial article often gives a slight response to these reactions.

It should contain between 14.5 and 16.5 per cent nitrogen and between 8.5 and 10.5 per cent of phosphorus.

Nuclein is dispensed both in the solid condition and in capsules. The solutions usually contain about 5 per cent of nucleic acid.

The metallic compounds of nuclein are prepared by adding solutions of the metals to an alkaline solution of the nuclein and precipitating the compound with alcohol.

Cuprol is a copper compound containing about 6 per cent of the metal. It is a greenish powder soluble in water, and is used as an astringent alterative, its special field being in ophthalmic practice.

Ferrinol, an iron nuclein compound, is a brown powder freely soluble

in water, containing about 6 per cent of iron and 4.5 per cent phosphorus combined in the nuclein. It is employed as a tonic and reconstructive.

Mercurol is a mercury compound, a colorless or brownish-white powder containing 10 per cent of mercury, soluble in water with a weak alkaline reaction. It is used internally and locally as a substitute for mercuric chloride and is recommended for syphilis.

Nargol is the silver compound of this series. It is a gonorrhea remedy and is recommended as a local application in all forms of diseases for which silver nitrate has been used. It is a light brownish-white powder, soluble in water and contains 10 per cent of silver.

Complex compounds of silver are prepared by treating the crude nuclein with formaldehyde and subsequently obtaining the silver compound by treating a soluble salt with silver nitrate which is dissolved in a solution of some neutral salt, and reprecipitated in a soluble form by alcohol.

Sophol

Sophol is a compound of silver and methylenenucleinic acid, the silver being in the organic (" masked ") form.

It is a yellowish powder, having a metallic taste and claimed to contain silver, equivalent to not less than 20 per cent metallic silver. It is readily soluble in water, the aqueous solution having a faint alkaline reaction; it does not give a precipitate on the addition of dilute solution of sodium hydroxide or of sodium chloride; it is insoluble in ether and alcohol.

If .5 gram sophol is boiled with 5 mils of sodium hydroxide solution, the latter assumes a black color with the development of a formaldehyde odor.

CHAPTER XIX

ETHEREAL SALTS—PHENOLS

ETHEREAL SALTS

The alcohols combine with organic and inorganic acids to form a large class of substances known as ethereal salts or esters. Many of these bodies are of great importance in medicine. Some of them, like the ethereal salts of the halogen acids, are identical with the monohalogen substitution products of the hydrocarbons. The di-, tri- and higher substitution products of the paraffins such as chloroform, $CHCl_3$, are not strictly ethereal salts, but their analogy and relationship is so close that they are conveniently considered under this heading.

We shall not undertake a description of all of these bodies, but will treat in full only those of interest to our work.

The ethereal salts are in general neutral in reaction, unless in exceptional cases only they may contain a free carboxyl or phenolic hydroxyl group. They are removable from acid or alkaline mixtures with immiscible solvents, and are hydrolyzed into their components by saponification with alcoholic potash. From the alkaline mixture the alcoholic portion can be separated by distillation or by shaking out with ether, and then on adding sulphuric acid, the acid constituent is freed, and may be recognized by appropriate tests.

Methyl Chloride

Methyl chloride, CH_3Cl, is the hydrochloric acid ester of methyl alcohol. It occurs, in the condensed state, as a colorless liquid, having an ethereal odor, and a sweet taste.

Methyl chloride is insoluble in water, more readily in alcohol, freely in ether and chloroform, and also in acetic acid. At about $-25°$ C. it has a specific gravity of .991, and boils at about $-21°$ C. It burns in air with a greenish flame, though it is not highly inflammable. The neutral solution is not precipitated by solution of silver nitrate, nor is there any reaction with potassium iodide and starch paste. In the liquid condition, it is a powerful refrigerating agent. At very low temperatures it forms with water a hydrate, $CH_3Cl \cdot 9H_2O$.

It is used as a general anesthetic mixed with ethyl chloride and ethyl bromide.

Methyl Iodide, CH_3I

Methyl iodide or iodomethane is a colorless, transparent liquid, which turns brown on exposure to the light. It boils 42° C., specific gravity 2.279 at 15° C. It is used as a vesicant and sometimes replaces cantharides in blistering compounds.

Methyl Acetylsalicylate, $C_6H_4(COCH_3)\cdot OCOCH_3$

This ester, known also as methyl rhodin and methyl aspirin, is a crystalline solid, melting 54°, insoluble in water, but dissolving in alcohol, ether, glycerin, and oils. It is employed as an antineuralgic

Methyl Benzoyl Salicylate

Benzosalin is methyl benzoyl salicylate, $C_6H_4\cdot O(CH_3)\cdot COO(C_6H_5CO)$, 1 : 2 the benzoyl salicylic acid ester of methyl alcohol.

Benzosalin is prepared by a reaction between the methylester of salicylic acid and benzoyl chloride in the presence of sodium hydroxide.

Benzosalin consists of fine, white crystals with a very faint aromatic odor. It melts at about 85° C. It dissolves readily in chloroform, benzene, and in 35 parts of 90 per cent cold alcohol. also in pure concentrated sulphuric acid.

Benzosalin passes the stomach unchanged and is decomposed into its constitutents, benzoic, and salicylic acid in the intestines.

It is said to be useful in rheumatic affections, such as arthritis, neuralgia, sciatica, and migraine, and in arthritis deformans.

Methyl Salicylate

Methyl salicylate has been fully discussed in connection with the chemistry of salicylic acid, page 687.

Methyl Gallate, $C_6H_2(OH)_3COOCH_3$

Methyl gallate or Gallicin forms grayish-white crystals, melting 192-202°, depending on its purity, soluble in water, alcohol, and ether. It is used as an antiseptic in eye troubles and as an anticatarrhal.

Methylenedimethyl Ester, $CH_2(OCH_3)_2$

Methylal, formal, or methylenedimethylate is a colorless volatile liquid with an odor resembling chloroform. Its specific gravity is .855 at 15°, it boils 42° C. and it is readily soluble in water, alcohol, and oils.

It has anesthetic, hypnotic, and anodyne properties, and is used in delirium tremens, insomnia, strychnin poisoning, acute gastric and intestinal indigestion. When dispensed as a local anesthetic it is usually in an ointment or liniment.

Methylene Dichloride, CH_2Cl_2

Methylene dichloride is an anesthetic resembling chloroform in its odor but boils at 40° and has a specific gravity of 1.377. It burns with a smoky flame and dissolves iodin with a brown color.

Mixtures of chloroform and alcohol are sometimes substituted for methylene dichloride, but the fraud is easily detected if the sample is diluted with water, and the precipitated heavy liquid tested for its specific gravity and boiling-point.

Ethyl Chloride, C_2H_5Cl

Ethyl chloride or hydrochloric ether is also known by several commercial names, e.g., kelene. It is used for general anesthesia by inhalation and as a local anesthetic.

It is a colorless, mobile liquid with a penetrating, pungent somewhat fragrant odor, boiling 12.5°, specific gravity .851 at 12° C., very volatile and inflammable, burning with a smoky green-edged flame and producing vapors of hydrogen chloride. It is slightly soluble in water, readily in alcohol and ether, and dissolves phosphorus, sulphur, fats, and oils. It combines with some of the metallic chlorides such as antimony pentachloride, and ferric chloride, to form crystalline compounds.

Baskerville [1] states that ethyl chloride intended for anesthetic purposes should have the following characteristics:

1. Its boiling-point should be +12.5°.

2. On allowing 30 mils to evaporate from a 12½ cm. filter paper, no foreign or unpleasant odor, especially a garlic odor (indicating phosphorus compounds) should be apparent either during or subsequent to evaporation.

3. Sixty mils when allowed to evaporate spontaneously should leave no weighable residue.

4. On shaking 10 mils with 10 mils water at 10° C., and then allowing the ethyl chloride to evaporate, no odor of acetaldehyde should develop on adding 3 drops of potassium bichromate followed by 5 drops of dilute sulphuric acid and boiling, nor should a bluish or greenish color develop.

5. Ten mils dissolved in 10 mils 95 per cent alcohol should give no turbidity or precipitate with 3 drops silver nitrate.

[1] J. Ind. and Eng. Chem., 1913, 5, 828.

The presence of ethyl chloride must be declared on the label of a package containing it, as it is a derivative of alcohol.

Its assay quantitatively is not a simple matter, because it must be saponified under pressure and there is so much gas developed that the ordinary form of pressure flask will not stand the strain. The result may be accomplished by using a Carius tube, and heating the mixture at the temperature of the water-bath. The little ampules should be scratched with a file at a point where they may be broken with comparative ease when subjected to concussion, and then introduced into the tube, followed by alcoholic potash. The tube can then be sealed off, the ampule broken by concussion, and after heating, the end of the tube is broken, the liquid washed out, the alcohol evaporated, and the chlorine determined by silver precipitation.

Polychlorated ethyl chloride, or Wigger's anesthetic ether, is a mixture of tri-, tetra- and pentachlorethane. It has an ethereal aromatic odor suggestive of camphor, and is used as an anesthetic and irritant. It is used chiefly in rheumatic conditions and neuralgia.

Ethyl Bromide

Ethyl bromide, C_2H_5Br, is the hydrobromic acid ester of ethyl alcohol containing approximately 1 per cent ethyl alcohol.

It is a colorless, strongly refractive, easily volatile liquid, having a pleasant ethereal odor. It is insoluble in water, but readily soluble in alcohol and in ether. It boils at from 38 to 40° C. Its specific gravity at 15° is 1.453 to 1.457.

It is stable when pure but when contaminated with ethyl iodide it becomes colored when exposed to light. It burns with difficulty. It is very difficultly saponified by potassium hydroxide and it is not attacked by sulphuric or nitric acids. Silver nitrate gradually precipitates silver bromide. If a mixture of 1 mil ethyl bromide, 5 mils alcohol and 10 drops of 15 per cent sodium hydroxide solution is heated to boiling, cooled, acidified with dilute sulphuric acid then shaken with chloroform and chlorine water added, a brown coloration will be produced in the chloroform layer. If equal volumes of ethyl bromide and sulphuric acid are shaken together in a bottle previously rinsed with sulphuric acid and closed with a glass stopper, the acid should not be colored yellow within an hour. After shaking equal volumes of ethyl bromide and water, no change of volume should occur in the two liquids, the water separated from the ethyl bromide should not have an acid reaction nor should it become turbid immediately on the addition of a drop of silver nitrate solution.

When a small portion is evaporated from a porcelain plate by causing it to flow to and fro over the surface little or no foreign odor is yielded as

the last portions pass off, and the plate is covered with a slight deposit of moisture.

One mil of ethyl bromin mixed with 3 drops of anilin and 2 mils of alcoholic solution of potassium hydroxide should not give off the odor of isonitrile even after warming. (Absence of chloroform.)

About 1 gram of ethyl bromide accurately weighed added to 30 mils of 80 per cent alcohol containing 2 grams silver nitrate will precipitate, after several hours, silver bromide, which when washed and dried should weigh 1.72 grams for each gram ethyl bromide used.

Ethyl bromide is a rapid anesthetic, acting much like chloroform.

Ethyl Iodide, C_2H_5I

Monoiodomethane or hydriodic ether is a clear, colorless neutral liquid becoming brown on standing. It boils 70 to 75°, specific gravity 1.94 at 15°, soluble in alcohol and ether but insoluble in water. It is employed as an antispasmodic, anesthetic, stimulant, and alterative, and is recommended in chronic rheumatism, scrofula, syphilis, bronchitis, and asthma. It is given internally and in the form of an ointment.

Ethyl Lactate, $C_3H_5O_3 \cdot C_2H_5$

Lactic ether is a colorless limpid liquid, sp. gr. 1.031 at 19° C., boiling 154° C., and soluble in water. It is employed as a sedative and hypnotic.

Ethylene Dichloride, $CH_2Cl \cdot CH_2Cl$

Ethylene chloride or Dutch liquid is, strictly speaking, an addition product of the unsaturated hydrocarbon ethylene, and is prepared by direct union with chlorine. It is a colorless oily liquid with pleasant odor and sweet taste, specific gravity 1.265 at 15° C., boiling 83 to 85°; its vapors are irritating to the membranes. It is soluble in alcohol, ether, and chloroform, and slightly in water.

It is used as a substitute for chloroform as an anesthetic, and externally is employed in rheumatism.

Monochlorethylene Chloride, $CH_2ClCHCl_2$

This product, also known as ethylene chloride, monochlorinated Dutch liquid, and vinyl trichloride, is a colorless liquid, having a pleasant odor, sp. gr. 1.458 at 9° C., boiling 114° and soluble in alcohol and water. It is used as an anesthetic in place of chloroform.

Ethylidene Chloride, CH_3CHCl_2

Ethylidene chloride is isomeric with ethylene dichloride. It is also termed chlorinated muriatic ether, alphadichlorethane, ethidene bichloride,

and chloridene. It is a colorless, oily liquid with a chloroform odor, sp. gr. 1.178 at 15° C., boiling 58–60° C., and used as an anesthetic and analgesic.

Ethyl Nitrite, $C_2H_5NO_2$

Ethyl nitrite or nitrous ether is known only in the form of the spirit of nitrous ether or sweet spirit of niter. The spirit is yellowish in color and has a fragrant, pungent odor. The official article contains not less than 4 per cent of the ester in alcoholic solution, and has a sp. gr. of .823 at 25° C., soluble in water and alcohol. It is also sold in a concentrated form which can be readily diluted with alcohol to the official strength.

Ethyl nitrite spirit is employed as a diaphoretic, stimulant, diuretic, antipyretic, and antispasmodic. It is used in fevers, colds, dropsy, colic, nausea, and genito-urinary troubles, and is almost always dispensed alone, but for dropsical complaints may be found mixed with squill, Digitalis, potassium acetate, or potassium nitrate. For certain states of febrile conditions it is mixed with aromatic spirit of ammonia.

Absolute ethyl nitrite is pale yellow, boiling 17–18° C., with sp. gr. .917 to .920 at 0°.

The assay of spirit of nitrous ether may be accomplished by the same procedure as is described under Amyl Nitrite. Factor for Ethyl Nitrite, 3.07.

Ethylene Dibromide, $CH_2Br \cdot CH_2Br$

Ethylene dibromide or dibromethane is formed by the direct union of bromin and ethylene. It is a colorless crystalline substance below 9° C. but is usually encountered as a colorless liquid with a chloroform odor, sp. gr. 2.189 at 15° C., boiling 129–131° C., miscible with alcohol, but insoluble in water.

It is used in epilepsy and neuralgia, but in small dosage as it is quite toxic.

Ethyl Acetate, $CH_3COOC_2H_5$

Ethyl acetate or acetic ether is a colorless fragrant inflammable liquid, boiling 72–77° C., miscible in all portions with alcohol and ether and with 17 parts of water.

The official grade contains about 10 per cent of alcohol and a little water. Ethyl acetate is sometimes used internally in nervous affections and to revive one after fainting. Externally it is used to a limited extent as an anesthetic and antirheumatic.

The odor of ethyl acetate is characteristic and the formation of this substance recognizable by its odor, is used as a test for acetic acid.

Ethyl Benzoate, $C_6H_5COOC_2H_5$

This ester is not used medicinally, but it plays an important part in analytical chemistry, as its formation as determined by its odor, is used as a test for cocain. It is volatile at all temperatures and boils 212–213° C.

Ethyl Cinnamate

Ethyl cinnamate occurs in storax; sp. gr. 1.0531, boiling 257–258°.

Ethyl Diiodosalicylate, $C_6H_2I_2(OH)COOC_2H_5$

Diiodosalicylic ether forms white crystals, melting 132°, soluble in alcohol and fixed oils and slightly in water. It is used in surgery as a substitute for iodoform.

Ethyl Formate, $HCOOC_2H_5$

Ethyl formate is a mobile, colorless liquid with a peach-kernel odor, sp. gr. .917 at 15° C., boiling 54°, miscible in all proportions with alcohol and ether and with 9 parts of water. It is used as an hypnotic and analgesic.

True ethyl formate must not be confused with a substance known as "orthoformic" ether, $CH(OC_2H_5)_3$, which is prepared from chloroform and sodium ethylate. This product is a colorless, aromatic liquid, boiling 145–146° C.

Ethyl Thiocarbimide, $C_2H_5 \cdot N \cdot CS$

Ethyl mustard oil is a colorless, pungent liquid, very irritant to the tissues and used externally as a local irritant in rheumatism, neuralgia and local pains. It boils 133° C.

Ethyl Valerate, $(CH_3)_2CHCH_2COOC_2H_5$

Isovaleric ether is a colorless liquid with a pleasant fruity odor, sp. gr. .871 at 15° C., boiling 134° C. It is used as a sedative and antispasmodic in nervous affections, especially asthma.

Amyl Nitrite, $C_5H_{11}NO_2$

Amyl nitrite is the isoamyl ester of nitrous acid. It is a yellow, transparent, very mobile, volatile, inflammable liquid having a penetrating characteristic odor, and a stimulating effect on the senses. Its sp. gr. is .870 to .880 at 15° or .865 to 875 at 25°, boiling 97 to 99°, evolving an orange-colored vapor, volatile at all temperatures, insoluble in water,

but dissolving in all the organic solvents. The ester deteriorates rapidly, and is usually dispensed in small hermetically sealed glass bulbs.

The commercial nitrite is probably contaminated with the nitrites of other higher alcohols, and furthermore the amyl radicle may be attributed to more than one isomeric form.

Assay, U. S. P. Method.—Transfer about 3 mils of Amyl Nitrite, which has been previously shaken with .5 gram of potassium bicarbonate and carefully decanted, to a tared 100-mil measuring-flask, containing about 20 mils of alcohol, and weigh it accurately. Add sufficient alcohol to bring the volume to exactly 100 mils and mix thoroughly. Introduce into a nitrometer exactly 10 mils of the alcoholic solution, followed by 10 mils of potassium iodide T. S., and afterward by 5 mils of diluted sulphuric acid. When the volume of gas has become constant (within thirty to sixty minutes), note the amount collected, multiply this volume in mils by 4.8 and divide the product by the original weight in grams of the Amyl Nitrite. At standard temperature and pressure, the quotient represents the percentage of Amyl Nitrite in the liquid. The temperature correction is one-third of 1 per cent of the total percentage just found for each degree—additive if the temperature is below 25° C., and subtractive if it is above 25° C. The barometric is four-thirtieths of 1 per cent of the total percentage just found for each millimeter—additive if it is above 760 mm. and subtractive if it is below 760 mm.

Assay, Modification of the U. S. P. Method.—Use a saturated salt solution in the nitrometer.

Weigh the amyl nitrite in a closed container and add 13 drops to about 2 mils of alcohol in the upper tube of the nitrometer and admit to the nitrometer tube. Wash out upper tube with 5 mils of alcohol. Then add a mixture of 10 mils of potassium iodide solution (1 : 10) and 10 mils N/1 sulphuric acid.

Allow reaction to cease before taking the reading of the NO. Compute this reading to normal pressure and temperature.

Weigh 1 mil NO at N.P.T. = .001306 gram.

From this the amount of amyl nitrite can be calculated.

If one is in any way familiar with drug products the physical properties of amyl nitrite are sufficient evidence for its detection.

It is a powerful cardiac stimulant and antispasmodic and is used by inhalation or in capsules for whooping cough, angina pectoris, asthma, tetanus, epilipsy, syncope, chloroform asphyxia, etc.

Amyl Bromide, $C_5H_{11}Br$

Amyl bromide is a clear, colorless liquid, sp. gr. 1.219 at 15°, boiling 120 °C., soluble in alcohol and used as a germicide and antiseptic.

Amyl Iodide, $C_5H_{11}I$

Amyl iodide is a yellowish liquid, sp. gr. 1.48 to 1.50 at 150° C., boiling 140 to 148° C., soluble in alcohol, used as a sedative and antiseptic.

Amyl Salicylate, $C_6H_4OH \cdot COOC_5H_{11}$

Amyl salicylate is a colorless or yellowish liquid, sp. gr. 1.055 to 1.065 at 15° C., boiling 263–265° C., soluble in alcohol, ether, and chloroform and insoluble in water. It is used both internally and externally as an antirheumatic.

Amyl Valerate

Amyl valerate, $CH_3 \cdot CH(CH_3) \cdot CH_2 \cdot COO(CH_3) \cdot CH_2 \cdot CH_2)$, is the iso-valeric acid ester of iso-amyl alcohol.

It is obtained by separating (by distillation) the ester which is formed when valeric acid or soluble valerate is added to a mixture of iso-amyl alcohol and sulphuric acid and the distillate obtained, washed, dried, and redistilled.

Amyl valerate is a colorless liquid, having when dilute an odor of apples. It is insoluble in water, soluble in alcohol, ether, and chloroform. It boils at 188 to 190° C. Its sp. gr. is .858 at 15° C.

Amyl valerate has been employed in the treatment of gallstone colic.

Amylene, $(CH_3)_2C = CHCH_3$

Amylene, trimethylethylene, or pental is a colorless, mobile inflammable liquid, with a disagreeable odor, sp. gr. .666 at 15° C., boiling 35–38° C., miscible with alcohol and ether, insoluble in water. It is used as an anesthetic in dental surgery.

Dimethylacetal, $CH_3CH(OCH_3)_2$

Dimethylacetal or ethylidenedimethylester is a colorless liquid, specific gravity .879 at 0°, boiling 62–63°, miscible with water and the organic solvents, and employed as an anesthetic as a substitute for chloroform.

Carbosant

Carbosant is santalyl carbonate, $(C_{15}H_{23}) \cdot O \cdot CO \cdot O \cdot (C_{15}H_{23})$, the carbonic acid ester of santalol.

It is an oily yellow fluid, almost tasteless and odorless, insoluble in water, and soluble in alcohol and ether. It contains 94 per cent of santalol.

Carbosant is saponified when heated with an alcoholic solution of caustic alkali with the production of potassium carbonate and santalol.

Carbosant is employed in the treatment of gonorrhea, cystitis, and prostatitis.

Nitroglycerin, $C_3H_5(ONO_2)_3$

Nitroglycerin, glyceryl trinitrate, propenyltrinitrate, or glonoin, is used in medicine as a remedy in angina pectoris. Its presence may be expected in remedies for heart troubles. It is commonly prepared for administration in the form of tablet triturates and pills containing from $\frac{1}{1000}$ to $\frac{1}{10}$ grain, and it is also mixed with Strophanthus or Digitalis, or both and occasionally with strychnin, spartein, Cactus grandiflorus, belladonna, and caffein. Spirit of glonoin is a pharmacopœial product and contains 1 per cent of nitroglycerin in alcoholic solution.

Nitroglycerin itself is a colorless or yellowish oil with a sweetish taste, sp. gr. 1.6, soluble in ether, sparingly in alcohol, and insoluble in water. It may be hydrolyzed by boiling alkalies, yielding glycerin and a nitrate, together with a small amount of nitrite owing to secondary reactions. On reduction with ammonium sulphide it yields glycerin, ammonia, and free sulphur.

Much work has been done on the assay of nitroglycerin tablets, and after an extended study Murray of the Bureau of Chemistry has recommended the following tests:

Methods for the Determination of Nitroglycerin in Medicinal Tablets.—*Preparation of the sample.*—Crush 25 tablets under 10 mils of ether. A 25-mil cylindrical graduate makes a convenient container and a stout glass rod is used to crush the tablets. Rinse the rod with a little ether, allow the insoluble material to settle and decant the solution into a 50-mil graduated flask. No special care need be taken to prevent a little insoluble material from going into the flask. Wash the residue repeatedly with 5-mil portions of ether and decant the washings into the flask until it has been filled to the mark. Insert the stopper and mix well.

Estimation by the Modified Scoville Method.—Place 20 mils of the ethereal solution in a carefully dried and tared 50-mil beaker. (A second aliquot of 10 mils may be used as a check.) Evaporate the solvent in a vacuum desiccator. Apply the vacuum gradually so as to prevent ebullition. Leave the beaker in the vacuum thirty minutes after the ether has evaporated. Weigh and calculate ether extract per tablet. Treat the residue with 2 mils phenoldisulphonic reagent, rotating the beaker in such a way that the reagent comes into contact with the entire inner surface. After ten minutes add water and wash into a 100-mil flask. (If a check analysis as suggested was made, wash this into a 50-mil flask.)

Dilute to the mark and place 10 mils, representing 1 tablet, in a 100-mil flask, add about 50 mils water and a few drops more potassium hydroxide solution (20 per cent) than is required to neutralize the acid. (Do not use sodium hydroxide.) Dilute to the mark and compare the color with that produced by a standard nitrate solution similarly treated. Use any convenient colorimeter or Nessler tubes.

Reagents and Standards.—*Phenoldisulphonic Acid Reagent.*—Dissolve 25 grams of pure white phenol in 150 mils of concentrated sulphuric acid, add 75 mils of fuming sulphuric acid (13 per cent SO_3), stir well, and heat for two hours at about 100°.

Standard Solution.—Dissolve .7217 gram pure KNO_3 in 1 liter of water. Evaporate 10 mils of this solution just to dryness on the steam-bath. Cool and treat the residue with 2 mils phenoldisulphonic acid reagent, observing the precautions noted above and using a glass rod if necessary to aid the solution of the residue. After five or ten minutes dilute to 250 mils. Each mil of this solution contains .004 mg. nitrogen. Add an excess of KOH solution to an aliquot of this solution and dilute to 100 mils. It is advisable to prepare a standard of approximately the same color as the unknown. Nitroglycerin is 5.4 times nitrate nitrogen.

Estimation by the Modified Hay Method.—Place 5 mils of the ethereal solution in a 50-mil beaker, dilute with 5 or 10 mils alcohol and add about 5 mils of $\frac{1}{2}$ per cent alcoholic potassium hydroxide. Cover with a watch-glass and allow to stand ten minutes. Place on a steam-bath, allow to boil, remove the watch-glass, and when most of the liquid is evaporated add about 25 mils water and leave on steam-bath until about half the liquid has evaporated or until the odor of alcohol can no longer be detected. Cool and dilute to 250 mils. Each mil of this solution represents .01 of a tablet. Introduce an aliquot representing .02 to .04 milligram nitroglycerin into a 100-mil graduated flask, dilute with sufficient water to make the volume 90 to 95 mils, add 1 drop concentrated hydrochloric acid, then 2 mils sulphanilic acid solution and 2 mils naphthylamine hydrochloride solution. Complete the volume with water. Prepare at the same time and in the same way standards containing known amounts of sodium nitrite. Stopper the flasks and mix well. Compare the colors after thirty minutes. Nitroglycerin is calculated by multiplying nitrogen found by 8.

Reagents and Standards.—*Sulphanilic Acid Solution.*—Dissolve 1 gram in 100 mils hot water.

Naphthylamine Hydrochloride Solution.—Under a hood boil .5 gram of the salt with 100 mils water for ten minutes, keeping the volume constant. Filter and keep in a glass-stoppered bottle.

Standard Solution of Sodium Nitrite.—To a cold solution of about 2 grams of sodium or potassium nitrite in 50 mils of water, add a solution

of silver nitrate as long as a precipitate appears. Decant the liquid and thoroughly wash the precipitate with cold water. Dissolve in boiling water. On cooling the silver nitrite is precipitated. Dry the crystals in the dark at the ordinary temperature (preferably in a vacuum). Weigh out 220 mg. of the dry silver nitrite, dissolve in hot water and decompose with a slight excess of sodium chloride. When the solution becomes clear, dilute to 1 liter. Dilute 5 mils of this solution to 1 liter. This second dilution is the standard to be used. It contains .0001 mg. nitrite nitrogen per mil.

Only nitrite free water should be used in the estimation by the modified Hay method.

Erythrol Tetranitrate

Tetranitrol, $C_4H_6(NO_3)_4$, is the tetranitrate of erythrite (butanetetrol), $C_4H_6(OH)_4$.

It forms colorless crystalline scales, insoluble in cold water, readily soluble in alcohol, melting at 61° C. (141.8° F.) On percussion it explodes much like nitroglycerin.

It is employed in angina pectoris and vascular diseases.

Nitroglucose

Nitroglucose is an explosive substance obtained by the action of nitric and sulphuric acid on glucose. It is marketed in either an alcoholic or aqueous solution of about 5 per cent strength, and is used in epilepsy, angina pectoris, and cardiac weakness.

CHLOROFORM, $CHCl_3$

Chloroform is used to a considerable extent as an anesthetic for inhalation, as a counter-irritant, a narcotic, and analgesic. For internal use it will be found in remedies for flatulent colic, gastralgia, asthma, cough, spasms, hysteria, hiccoughs, scarlet fever, insomnia, and for removing gallstones.

Externally it is administered in the form of liniments for rheumatism, neuralgia, colic, etc., and hypodermically for hydrocele. Chloroform is also used to a limited extent in some of the artificial flavors used in foods.

The general run of cough mixtures contain in addition to the chloroform, white pine bark, wild cherry, sassafras, Sanguinaria, spikenard, balsam poplar buds, eriodictyon, and sometimes morphin; or sometimes this may be varied by substituting codein and Cannabis indica. Compound tincture of opium or diarrhea mixture contains opium, camphor, Capsicum, and chloroform. Chloranodyne and preparations of the chlorodyne type contain chloroform with morphin, Cannabis, hydrocyanic

acid, Capsicum, and peppermint. Chloroform is employed to a considerable extent in throat lozenges.

Spirit of chloroform also called chloric ether, consists of about 10 per cent of chloroform and 90 per cent of ethyl alcohol by weight. Chloroform water or aqua is official in some of the pharmacopœias, and is a saturated aqueous solution of chloroform. Emulsions of chloroform are made with tragacanth, oil of almond, egg yolk, sometimes with the addition of camphor. Chloroform liniment is prepared with about 70 per cent of soap liniment and 30 per cent of chloroform.

Chloroform is a colorless, heavy mobile liquid with a characteristic odor. Its sp. gr. is 1.49887 at 15° C. and it boils at 60 to 61°, according to Baskerville. The anesthetic chloroform on the American market runs in specific gravity from 1.4730 to 1.4827 at 25° C. It is not inflammable, but its heated vapor burns with a greenish flame. It is only slightly soluble in water, but is miscible with alcohol and ether, and it is an excellent solvent, dissolving many of the alkaloids, resins, fats, gutta percha, caoutchouc, balsams, gum chicle, etc.

Chloroform is readily decomposed by warm alcoholic potash, yielding potassium formate and chloride. It gives the carbylamine reaction when treated with anilin and alcoholic potash. When brought in contact with a solution of alpha- or beta-naphthol in strong potassium hydroxide and heated to 50° C. a fine blue color is developed, changing in contact with air to blue green, green, green brown and brown. The specifications for chloroform intended for anesthetic purposes have been laid down by Dr. Baskerville [1] as follows:

1. When 100 mils are evaporated over the steam-bath until 10 mils remain and the last portions are then allowed to evaporate spontaneously from a piece of filter paper, there should result no odor of fusel oil, empyreumatic matter, or other substances than chloroform and alcohol.

2. One hundred mils should leave no weighable residue on evaporation.

3. When 20 mils are mixed with 15 mils of concentrated sulphuric acid in a glass-stoppered tube of 50 mils capacity previously rinsed with concentrated sulphuric acid, no visible coloration should be imparted after the addition of .4 mil of pure 40 per cent formaldehyde solution, and then shaking thoroughly for five minutes. (Test for organic impurities.)

4. When 20 mils of the sample are boiled over 1 gram of clean crystals of calcium carbide, and the vapors evolved are passed into ammoniacal silver nitrate solution, no acetylene reaction should result. Absence of water.

5. Anesthetic and commercial chloroforms will contain a small quantity of alcohol. If it is desired to test for alcohol in a product of higher purity

[1] J. Ind. and Eng. Chem., 4, 1912, 576.

than the above mentioned, 10 mils are shaken in a separatory funnel with 4 mils of concentrated sulphuric acid, the treatment repeated, and a third time with 2 mils. The acid solution is then mixed with 40 mils of water and the dilute solution gently distilled until 20 mils have passed over. Ten mils of the distillate are treated with 6 drops of 10 per cent potassium hydroxide, warmed to 50° C., a saturated solution of iodide in potassium iodide added drop by drop, with agitation until the liquid becomes permanently yellowish brown in color, when it is carefully decolorized with potassium hydroxide. No iodoform should be deposited. This test is not peculiar to alcohol, being produced also by acetaldehyde, propyl alcohol, acetone, etc., but pure chloroform should give a negative test.

6. Pure chloroform complying with the iodoform test is free from acetone. Anesthetic chloroform should give a negative test when the following procedure is applied: Ten mils of the sample are agitated with 5 drops of .5 per cent sodium nitroprusside and 2 drops ammonium hydroxide (sp. gr. .925) and the mixture allowed to stand for several minutes. Chloroform containing up to 1 per cent of alcohol may impart a yellowish-brown color to the supernatant liquid on agitation, but when acetone is present an amethystine color results. The test must be conducted in the cold.

After application to the suspected chloroform direct, the first 10 per cent distillate and the 10 per cent residuum obtained by allowing 100 mils of the sample to distill slowly should be tested. When the proportion of acetone to chloroform is 1 : 500, the amethyst color is marked, but in the presence of 1 : 1000 the coloration is not distinct until the whole mixture has been saturated with ammonium sulphate, shaken, and allowed to rest for five minutes. It is advisable to run a blank test on pure anesthetic chloroform for comparison.

Some acetaldehyde is generally present in fresh and properly stored samples of anesthetic chloroform in portions greater than 1 : 3300; usually the reaction is not interfered with by this substance, but in every case the sample should be examined for the presence of acetaldehyde and if it complies with test 7(*a*) below, a positive reaction upon applying the acetone test may be said to be solely indicative of acetone.

7. The presence of 3 parts of acetaldehyde by volume in 1000 parts of chloroform may be detected by the following reaction and smaller amounts by resorting to fractionation, and chloroform of all grades should comply with the test (*a*).

(*a*) Five mils of the sample are agitated with 5 mils of there agent of Francois (20 mils of sulphurous acid, 30 mils 1 : 1000 rosanilin acetate solution and 3 mils sulphuric acid) in a glass-stoppered tube; no coloration should result even after fifteen minutes.

(*b*) Pure chloroform giving a negative reaction in Test 5 may be

regarded as free from acetaldehyde; but it should also give no response when 5 mils are agitated with 5 mils Nessler's reagent, U. S. P. and the mixture allowed to stand five minutes.

When 10 mils of anesthetic chloroform are agitated with 10 mils of water and 5 drops Nessler's reagent U. S. P., and the mixture then allowed to stand for five minutes, there should result no precipitate and the reagent should assume no coloration, though it may become opalescent or slightly turbid.

8. When 20 mils of either pure or anesthetic chloroform are thoroughly agitated with 10 mils of water and 2 drops of phenolphthalein solution, and then titrated with N/100 potassium hydroxide solution, added drop by drop, not more than .2 mil of standard alkali should be required to produce a faint but decided alkaline reaction permanent for fifteen minutes, when the mixture is shaken for thirty seconds after the addition of each drop of alkali.

9. The following tests are conducted in order to detect the decomposition products of pure chloroform:

(*a*) *Carbonyl Chloride.*—To 15 mils of the sample contained in a 25-mil dry glass-stoppered tube, sufficient of a perfectly clear 1 : 19 barium hydroxide solution is added to fill the tube. After allowing the mixture to stand three hours in a dark place without agitation, the observation as to the formation of a film of barium carbonate is made.

(*b*) *Hydrochloric Acid and Chlorides.*—Samples complying with 8 are assuredly free from carbonyl chloride, hydrochloric acid and chlorine, but pure and anesthetic chloroform should also comply with the following test: When 10 mils of the sample are agitated with 5 mils of water for five minutes the water extract should not become turbid or give any precipitate on adding silver nitrate solution (absence of hydrochloric acid or chlorides) and no reduction should occur on warming (absence of acetaldehyde, formic acid and formates).

(*c*) *Chlorine and Hydrogen Dioxide.*—When 10 mils of the sample are agitated during fifteen minutes with 10 mils of a 10 per cent cadmium potassium iodide solution no iodin should be liberated, as determined by the addition of starch solution. Chloroform of all grades should give a negative reaction with this test.

10. The decomposition products of anesthetic chloroform.

(*a*) The detection of acetaldehyde has been referred to in 7.

(*b*) Anesthetic chloroform failing to comply with 8 should be rejected.

(*c*) When 20 mils of the sample are shaken during twenty-five minutes with 15 mils of concentrated sulphuric acid in a 50-mil glass-stoppered tube previously rinsed with sulphuric acid, and 2 mils are diluted with 5 mils of water, the liquid should remain colorless and clear and should possess no odor foreign to anesthetic chloroform; and the liquid should

retain its transparency and colorless state when further diluted with 10 mils of water and the transparency should not be diminished on adding 5 drops of silver nitrate solution.

Detection and Estimation of Chloroform.—As chloroform is one of the inhibited drugs, its presence in medicinal preparatioms and in food products must be declared on the label.

In many cases the characteristic odor will indicate that chloroform is present, but of course in others it will be masked by more powerful odors, and the peculiar cooling effect which it imparts on inhalation may be confused with that given by menthol.

From liquid mixtures chloroform may be obtained by distillation and on diluting the distillate sufficiently if alcohol is present, the chloroform will settle out in the bottom of the flask. By distilling with steam, this procedure may be made approximately quantitative. The heavy liquid which has settled out should be tested further by applying the phenyl isocyanide test, and determining its boiling-point. Chloroform boils 60 to 61°, bromoform 148 to 150°, and carbontetrachloride 76 to 77°. The latter does not give the phenylisocyanide test.

Chloroform can be determined when it occurs in liquid products by distilling into a flask, diluting the distillate with water if much alcohol is present, and decanting most of the supernatant liquid. The chloroform is then treated with 15 to 25 mils of N/1 alcoholic potash and boiled for one to two hours under a reflux. The chlorine is then determined by precipitating with silver nitrate in presence of nitric acid and the chloroform calculated.

With some distillates it might be more desirable to add the alcoholic potash without previous dilution and decantation.

Dowzard's [1] method for the determination of chloroform in lozenges is as follows: A weighed lozenge is digested with 70 mils alcoholic potash in a 200-mil flask with reflux condenser, warming until dissolved and then gently boiling forty-five minutes. Twenty-five mils of water are added and a few drops of phenolphthalein, the solution acidified with nitric acid and then neutralized with calcium carbonate. After cooling the chlorine is titrated with silver nitrate solution, using potassium chromate. A blank may be run, using the same quantities of reagents without the lozenge, and the difference in amount of chlorine calculated to chloroform.

Patents have been obtained for a " solid " chloroform which is prepared by mixing the substance with peptone and allowing the excess to evaporate.

[1] Am. J. Pharm., 80, 1909, 511.

Bromoform, $CHBr_3$

Bromoform, tribromomethane, methenyl tribromide, also called "formyl tribromide," is a heavy colorless liquid with an odor resembling chloroform. Its sp. gr. is 2.829 to 2.833 at 15° C., or 2.808 at 25° C., boiling 148 to 150 and solidifying 6° C. It is soluble in alcohol and ether, somewhat in glycerin, and almost insoluble in water.

It is not used to any great extent, but is an anesthetic, nervine, and sedative, and is employed chiefly in whooping cough.

It gives the phenylisocyanide test, but its high specific gravity and boiling-point distinguish it sharply from chloroform.

Brometone. Tribrom-Tertiary-Butylalcohol—Acetone-Bromoform

Brometone, $CBr_3 \cdot C(OH)(CH_3) \cdot CH_3$, is produced by the reaction of acetone on bromoform in the presence of caustic alkalies.

It occurs in fine white, prismatic crystals melting 167°, which possess a camphoraceous odor and taste. It is slightly soluble in water, soluble in alcohol, ether, benzine and most organic solvents.

Brometone is claimed to have the sedative action of the bromides without the disadvantages of producing bromism.

Trichlorisopropyl Alcohol. $CCl_3 \cdot CH = CH_3OH$

This substance, known as Isopral, occurs in prismatic crystals, with a camphoraceous odor and pungent taste, melting 49° C., soluble in water, alcohol, and ether. It is employed as an hypnotic and as a substitute for chloral. In its appearance and organoleptic properties it bears a close resemblance to chloretone.

Fluoroform, CHF_3

Fluoroform is dispensed in an aqueous solution containing about 3 per cent of the drug in water, known as Fluoroformol or Fluoryl. It is odorless and tasteless and is used as an internal antiseptic, alterative, and tuberculocide. It is recommended for consumption and pneumonia.

IODOFORM, $CHCl_3$

Iodoform or tri-iodomethane, famous for its powerful and clinging odor, is formed when ethyl alcohol (not methyl), acetone, aldehyde, and other simple organic substances containing oxygen united with a $CH \cdot C$ group are warmed with alkali or an alkaline carbonate.

It is used to a large extent as an antiseptic, and though attempts are often made to disguise its presence, its odor will usually be revealed to the operator before he has proceeded far with his investigations.

It crystallizes in yellow six-sided plates, melting 115 to 119°, and at higher temperatures emitting vapors of iodin, sublimable with ease and volatile at the ordinary temperature, and with steam. It is very slightly soluble in water and petroleum ether, fairly soluble in alcohol, and readily in chloroform, ether, fixed and volatile oils. When boiled with alcoholic potash it is converted to potassium iodide and formate.

Iodoform gives the carbylamine reaction when heated with aniline and alcoholic potash. When dissolved in chloroform and a crystal of lead nitrate added, a light rose color appears turning to deep rose and red. Bromoform gives on warming a wine red color passing gradually to garnet-red and finally to reddish-brown.

Iodoform unites with many organic bases and sulphocompounds, forming definite crystalline compounds, many of which possess antiseptic or other therapeutic properties, but have not the characteristic penetrating odor of iodoform.

Estimation of Iodoform.—The determination of iodoform is readily accomplished by boiling for an hour with alcoholic potash under a reflux, evaporating the bulk of the alcohol, diluting with water, acidifying with dilute nitric acid, precipitating with silver nitrate, and filtering the silver iodide onto a Gooch.

When working with gauzes or bandages, the sample is introduced into a capacious Erlenmeyer, covered with alcoholic potash and boiled for an hour under a reflux. The liquid is then decanted, and the textile washed with hot alcohol, which is added to the alkaline liquid, and then evaporated, the residue taken up with water, acidified with dilute nitric acid, filtered if necessary, and the iodin precipitated with silver nitrate.

Ointments containing iodoform can be similarly treated, but it will be necessary, after acidifying, to shake out any oil or separated acid with ether. The clear aqueous liquid is then drawn off, the ether expelled by gentle heat, and the iodin precipitated with silver nitrate.

Iodoform will sometimes be found in pills, either alone or with iron and quinin; also in globules with cod-liver oil; and in oily inhalants with creosote, eucalyptus, etc.

In order to present iodoform in a condition where it will be less objectionable, various products have been proposed. Aromatized or deodorized iodoform is a National Formulary product, prepared by mixing iodoform with 4 per cent of coumarin.

Iodoformin is a product obtained by treating iodoform with hexamethylenetetramine and contains 75 per cent of iodoform.

Iodoformogen or Diodoform albuminate is a yellow, fine dry powder,

about three times as voluminous as the same weight of iodoform and nearly odorless. The iodoform is liberated on contact with the wounded surface.

Ethylene Tetraiodide. Diiodoform, C_2I_4

Diiodoform crystallizes in yellow needles, odorless when pure, but gradually decomposing on exposure to the light, with the development of a characteristic odor. It melts 187° C., is readily soluble in chloroform and benzol, slightly in alcohol and ether, and insoluble in water. It is sometimes used instead of iodoform.

Iothion, $CH_2ICHOHCH_2I$

Iothion or diiodohydroxypropane is obtained by heating dichlorhydrin with potassium iodide in the presence of water.

It is a yellowish, oily, heavy liquid, of sp. gr. 2.4 to 2.5, containing 77 per cent of iodin. It is volatile at the body temperature and not unpleasantly odorous. It is insoluble in water but soluble in glycerin, oils, alcohol, and other organic solvents. It is incompatible even with weak alkalies.

If iothion is heated on the water-bath under a reflux condenser for five to six hours, with 33 per cent solution of potassium hydroxide and the iodin liberated from the residue by sulphuric acid and sodium nitrate and extracted with carbon disulphide, the titration of this iodine carbon disulphide solution with sodium thiosulphate in the usual way should indicate 77 per cent of iodin.

Iodanisol, $C_6H_4OCH_3I\cdot(1\cdot2)$

Iodanisol, or anisol orthoiodide, is a heavy yellow liquid, sp. gr. 1.8 at 20°, boiling 240° C., insoluble in water, but soluble in alcohol, ether, and chloroform. It is an antiseptic and is sometimes used as a substitute for iodoform, and is also a local irritant.

MERCAPTANS AND THEIR DERIVATIVES

Alcohols form two classes of compounds with hydrogen sulphide, the hydrosulphides RSH and the sulphides R_2S. The former are called mercaptans on account of their combining readily with mercuric oxide, forming crystalline compounds. The hydrosulphides or sulphhydrates, as they are sometimes called, may be regarded as sulphur- or thioalcohols, and the organic sulphides as thio-ethers.

Ethyl Mercaptan, C_2H_5SH

Ethyl mercaptan may be obtained by treating alcohol with phosphorus pentasulphide, and by distilling a concentrated solution of ethyl potassium sulphate with potassium hydrosulphide.

$$5C_2H_5OH + P_2S_5 = 5C_2H_5SH + P_2O_5$$

$$C_2H_5KSO_4 + KSH = C_2H_5SH + K_2SO_4$$

It is a colorless, unpleasant, garlic-smelling liquid, boiling 36°, it burns with a blue flame, is sparingly soluble in water but dissolves readily in alcohol and ether. It is very volatile and a drop exposed to the air soon solidifies on account of the lowering of the temperature due to the evaporation.

It is unaffected by caustic alkalies, but sodium or potassium displace hydrogen, forming the mercaptides C_2H_5SM, which are crystalline bodies soluble in water.

Mercuric oxide reacts with mercaptan, evolving much heat and forming a white crystalline inodorous compound, $(C_2H_5S)_2Hg$, which is insoluble in water, but may be crystallized from alcohol or strong hydrochloric acid. It is unaffected by potash. On oxidation with nitric acid mercaptan is converted into an ethyl sulphuric acid, $C_2H_5SO_2OH$. The sulphonic acids formed on oxidation of the mercaptan are relatively strong, and their salts differ from the sulphide in not being hydrolyzed when boiled with dilute aqueous potash.

Ethyl mercaptan is not a medicinal agent, but it forms the starting-point of a number of important hypnotic drug products, including sulphonal, trional, and tetronal. These bodies are all obtained by subjecting ethyl mercaptan and an appropriate ketone to the action of dry hydrogen chloride, when condensation takes place and a mercaptol results. On oxidizing the latter with permanganate the hypnotic is obtained. Acetone gives sulphonal, methyl ethyl ketone gives trional, diethyl ketone gives tetronal.

Sulphonal, $(CH_3)_2C(SO_2C_2H_5)_2$, Diethylsulphonedimethylmethane

Sulphonal forms colorless, odorless, tasteless, prismatic crystals, melting 125.5°, slightly soluble in cold water, but dissolving without difficulty in boiling water, alcohol, ether, chloroform, and benzol. When heated with charcoal, mercaptan is evolved, recognized by its garlicky odor, and when heated with sodium acetate, hydrogen sulphide is evolved.

Trional, $(CH_3)(C_2H_5)C(SO_2C_2H_5)_2$, Diethylsulphonemethylethylmethane

Trional forms colorless, lustrous, odorless, crystalline scales, melting 74 to 76° C., fairly soluble in cold water, more readily in boiling water, alcohol, and ether. When heated with charcoal or sodium acetate it gives the same characteristic tests as sulphonal.

Tetronal, $(C_2H_5)_2C(SO_2C_2H_5)_2$, Diethylsulphonediethylmethane

Tetronal forms colorless lustrous laminæ, with camphoraceous odor and bitter taste, melting 85°, slightly soluble in water, soluble in alcohol and ether.

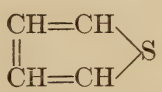
These three bodies are used as hypnotics and sedatives and usually by themselves in the form of pills, tablets, capsules, or powders. They do not give any well-defined color or precipitation tests, but in the general scheme of qualitative analysis they will appear on shaking out an acid aqueous solution with petroleum ether and ether. In the absence of tests indicating other ingredients, portions of the residue should be tested by ignition first with charcoal and then with anhydrous sodium acetate, and if the mercaptan odor is developed in the former and hydrogen sulphide in the latter, a melting-point determination should be run on the recrystallized substance, and the identity of the individual can then be established.

ESTERS OF AROMATIC ALCOHOL

The esters of the aromatic alcohols have practically no use in medicine. Benzyl chloride, iodide, sulphide, and benzyl dichloride are all well characterized individuals.

The cinnamyl and benzyl esters of cinnamic and benzoic acids are of importance in this work, as they occur in the aromatic balsams and the chemistry of the latter is in large part concerned with the properties of the esters.

Thiophene



Thiophene, one of the constituents of coal tar, occurs as an impurity in benzol, and may be separated therefrom by shaking with concentrated sulphuric acid. If the acid contains a trace of isatin (an oxidation product of indigo) a blue color develops which is known as the indophenin reaction.

Thiophene is sometimes used as an antiseptic.

Thiophene Diiodide, $C_4H_2I_2S$

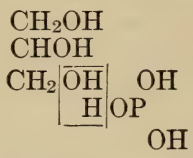
Thiophene diiodide or biniodide in a yellow crystalline substance melting about 40° C., soluble in alcohol, ether, and chloroform, and used as an antiseptic.

Thiophene Tetrabromine, C_4Br_4S

This derivative of thiophene is a yellow powder, melting at 112° C., and used as an antiseptic.

THE GLYCEROPHOSPHATES

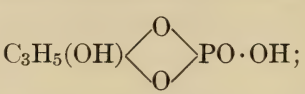
Glycerophosphoric acid, as prepared commercially, is a partially esterified glycerin compound with phosphoric acid. It is probable that only one hydroxyl takes part in the reaction and that two replacable hydrogens of the phosphoric acid remain free.



The salts of glycerophosphoric acid were introduced as nerve foods and tonics and have become very popular. The most important salts found on the market are those of calcium, sodium, and potassium. To a lesser extent we meet with those of iron, manganese, quinin, and strychnin.

The glycerophosphates are usually dispensed in the form of elixirs, though sometimes they are given in capsules and of late the manufacture of albumin compounds soluble in water is claimed by processess which consist in mixing albuminoids (milk casein or vegetable casein) suspended in dilute alcohol with the requisite quantity of a glycerophosphate, expelling the alcohol by heat and drying; or in mixing the albuminoid with a dilute solution of the glycerophosphate, filtering, evaporating to dryness, or precipitating with alcohol. Such products are probably more of the nature of mixtures than chemical individuals.

Power, Tutin, and Hann,[1] as the result of an interesting research on the glycerophosphoric acids, conclude that the only known products of the reaction between glycerin and phosphoric acid are the monoester (glycerylphosphoric acid), $C_3H_5(OH)_2 \cdot O \cdot PO(OH)_2$; the diester,



[1] Trans. Chem. Soc., 1905, 249 and 1906, 1749.

and the triester (glycerylphosphate), $C_3H_5PO_4$. The first form can have the unsymmetrical structure

$$\begin{array}{lll} CH_2\cdot O\cdot PO_3H_2 & & CH_2OH \\ CH\cdot OH & \alpha\text{-acid or the symmetrical} & CHOPO_3H_2 \quad \beta\text{-acid} \\ CH_2OH & & CH_2OH \end{array}$$

Their investigations indicate that the synthetic product is a mixture of the α- and β-acids, and that this differs from the acid obtained from lecithin only by a difference in proportion of the components.

Glycerophosphoric acid behaves toward methyl orange as a monobasic acid and toward phenolphthalein as a dibasic acid, similarly to phosphoric acid.

Falières [1] has worked out a titration method for estimating glycerophosphates which is applicable to the calcium salt: The determination is carried out by dissolving .2 gram of the salt in a little water, adding 20 mils of decinormal oxalic acid, and making up to 100 mils. Fifty mils of the filtrate, containing the free glycerophosphoric acid, and an excess of oxalic acid, are titrated with decinormal potash and phenolphthalein and twice the number of mils required = A. The calcium oxalate remaining on the filter, after well washing with boiling water, is dissolved in dilute nitric acid (1 : 10), a few drops of sulphuric acid are added, and the solution is titrated with decinormal permanganate = B. The quantity of lime is expressed by $B\times.0028$, and for 100 grams of glycerophosphate $= B\times.0028\times5\times100$. The formula $A+B-20$ gives in mils of decinormal potash, the weight of the glycerophosphoric acid contained in .2 gram of the substance, while $(A+B-20)\times.0086\times5\times100$ gives the percentage amount of glycerophosphoric acid in the calcium glycerophosphate.

The neutral organic glycerophosphates and the double salts are all amorphous. In the dry state they are stable, but when heated with water they decompose. Quinin glycerophosphate on heating in aqueous solution, gives on cooling a white precipitate of quinin phosphate.

For some time the sodium and potassium glycerophosphates were known only in a concentrated solution having the consistency of honey, but a highly purified dry sodium salt has recently been put upon the market.

The laboratory of the American Medical Association has made a thorough study of some of the glycerophosphates, and their results quoted below give a very accurate description of the properties of the calcium and sodium salts.

[1] Repert. Pharm., 1898, 10, 8.

Calcium Glycerophosphate

Calcium glycerophosphate is monohydrated calcium glycerophosphate, $Ca(C_3H_5(OH)_2)PO_4$, H_2O, the normal calcium salt of glycerophosphoric acid, $H_2(C_3H_5(OH)_2)PO_4$, containing not less than 90 per cent of anhydrous normal calcium glycerophosphate.

Calcium glycerophosphate is a fine white powder, odorless and almost tasteless; somewhat hygroscopic.

It is slightly (about 1 : 400) soluble in water; almost insoluble in boiling water; easily soluble in dilute acids; insoluble in alcohol or in ether.

The aqueous solution is alkaline to red litmus paper. A cold, saturated, aqueous solution yields white, iridescent scales when heated to boiling (anhydrous calcium glycerophosphate).

At about 130° C. calcium glycerophosphate loses its water of hydration. When heated above 170° C. the salt is decomposed with evolution of inflammable vapors, and at a red heat it is converted into calcium pyrophosphate.

On the addition of ammonium oxalate solution, the aqueous solution yields a white precipitate, insoluble in acetic acid or in a solution of citric acid, but soluble in hydrochloric acid. With lead acetate solution the aqueous solution yields a white precipitate which is soluble in nitric acid.

If 1 gram of calcium glycerophosphate is dissolved in 10 mils of diluted nitric acid and an equal volume of ammonium molybdate test solution be added, no precipitate should be formed within one hour.

If 1 gram of calcium glycerophosphate is dissolved in 100 mils of 1 per cent hydrochloric acid, the solution should not respond to the U. S. P. time-limit test for heavy metals.

If .1 gram of calcium glycerophosphate is dissolved in 10 mils of diluted nitric acid and 1 mil of silver nitrate solution added, not more than a distinct opalescence should appear within one minute.

If .1 gram of calcium glycerophosphate is dissolved in 10 mils of diluted hydrochloric acid and 1 mil of barium chloride solution added, no distinct turbidity should appear within one minute.

If 1 gram of calcium glycerophosphate in water is titrated with N/10 potassium hydroxide, using phenolphthalein as indicator, not more than 1.5 mils of the alkali should be required.

If 1 gram of the finely powdered salt is shaken with 25 mils of alcohol, the mixture filtered, the filtrate evaporated on the water-bath and the residue dried for one hour at a temperature not exceeding 70° C. the residue should weigh not more than .01 gram.

If from .5 to 1 gram of the finely powdered salt is dried to constant weight at 130° C., the loss should not exceed 10 per cent.

If from .3 to .5 gram of anhydrous calcium glycerophosphate is weighed into a Kjeldahl flask, 10 mils of a mixture of equal parts of fuming nitric acid and concentrated sulphuric acid added, the mixture heated until oxidation is complete, a little more fuming nitric acid being added if necessary, the solution diluted with 50 mils of water and the phosphorus determined in the usual way, by precipitation with ammonium molybdate and final weighing as magnesium pyrophosphate, the weight should correspond to from 14.16 to 14.75 per cent of phosphorus.

If from .3 to .5 gram of anhydrous calcium glycerophosphate is dissolved in 20 mils of a 5 per cent solution of citric acid, 80 mils of water added, the calcium precipitated as oxalate in the usual way and weighed as calcium oxide, the calcium oxide should correspond to from 18.7 to 19.8 per cent of calcium.

Sodium Glycerophosphate

Sodium glycerophosphate is hydrated sodium glycerophosphate, $Na_2(C_3H_5(OH)_2)PO_4 \cdot 5\frac{1}{2}H_2O$.

At about 60° C. it begins to lose its water of hydration; when strongly heated the salt yields inflammable vapors and at a red heat is converted into sodium pyrophosphate.

The aqueous solution (1 in 20) is alkaline to litmus and to phenolphthalein.

If an aqueous solution (1 in 20) is acidified with nitric acid, and an equal volume of cold ammonium molybdate solution added, it should remain clear for one hour. On heating, however, a yellow precipitate will be formed.

The aqueous solution (1 in 100) acidified with hydrochloric acid, should not respond to the U. S. P. VIII time limit test for heavy metals.

The aqueous solution (1 in 100) acidified with hydrochloric acid on addition of barium chloride solution should show no distinct turbidity within one minute.

The aqueous solution (1 in 100) acidified with nitric acid should not show more than a slight opalescence with silver nitrate solution.

The aqueous solution (1 in 100) acidified with acetic acid should not become turbid within one minute on addition of ammonium oxalate test solution.

If 1 gram of sodium glycerophosphate is thoroughly triturated in a mortar with 20 mils of alcohol, the liquid filtered and the alcoholic solution evaporated spontaneously the residue, after drying over sulphuric acid, should correspond to not more than 1 per cent of the weight of the salt taken.

If 2 to 3 grams of the salt is weighed, dissolved in distilled water and

the solution titrated with half-normal hydrochloric acid, using methyl orange as indicator, the acid consumed should correspond to not less than 99 per cent of hydrated sodium glycerophosphate.

The pure glycerophosphates in aqueous solution are not precipitated by heat, but are thrown out by alcohol and ether. They give no immediate precipitate with ammonium phosphomolybdate, magnesium mixture, nor uranium acetate. The white silver nitrate precipitate is soluble in excess of water. The white precipitate given by lead acetate is soluble in acetic acid.

The presence of glycerophosphates in admixtures is usually indicated by the non-appearance of a precipitate with ammonium molybdate in the cold after considerable time, and a heavy precipitate with the same reagent after another portion has been boiled with nitric or hydrochloric acid. This test, however, is open to objection if one is working with solutions containing a considerable amount of sugar. It is best to make a preliminary test with magnesium mixture which will throw out phosphates readily even in presence of sugar or oxalic acid. If no precipitate is obtained, and on subsequent boiling with nitric acid, neutralizing and adding magnesium mixture, a white precipitate comes out which is soluble in dilute nitric acid and gives a yellow precipitate with ammonium molybdate, the presence of glycerophosphates is established.

The glycerophosphates resemble the hypophosphites when subjected to a high temperature in an ignition tube, for they evolve inflammable vapors. They differ from them, however, in their reaction with silver nitrate, for while the hypophosphites give a permanent precipitate which soon turns black, the glycerophosphate compound is soluble in water.

If it is desired to determine quantitatively the amount of glycerophosphates in a mixture, the solution should first be neutralized with ammonia and an excess of magnesia mixture added to precipitate any free phosphate. After filtering and washing, the solution is acidulated with nitric acid and boiled under a reflux for an hour or two. The solution is filtered if necessary, treated with excess of ammonia, and precipitated with magnesia mixture. The precipitate is filtered and washed, dissolved in dilute nitric acid, precipitated with ammonium molybdate at 60 to 80° C., the precipitate washed with hot water, dissolved in ammonia water, the solution precipitated with magnesia mixture and allowed to stand overnight. The ammonium magnesium phosphate is then filtered, washed with dilute ammonia, ignited, and weighed as magnesium pyrophosphate. By calculating back the amount of glycerophosphoric acid or its salt may be obtained.

PHENOLS

Phenols are hydroxy-compounds of the aromatic series in which the hydroxyl group is attached to the nucleus. They are classed as mono-, di-, trihydric, etc., according to the number of hydroxyls present. Carbolic acid and the three isomeric cresols or hydroxytoluenes are monohydric, resorcinol and its isomers are dihydric, and phoroglucinol is a trihydric phenol.

Most phenols are colorless crystalline substances, some possessing a characteristic odor, readily soluble in alcohol and ether and to some extent in water, the solubility increasing with the number of hydroxyl groups. The monohydric members volatilize readily, while the trihydric phenols usually are decomposed on heating, and distill only moderately with steam.

Phenols yield a violet, blue, or green color with ferric chloride, the particular color depending in the case of the di- and trihydric compounds on the relative positions of the hydroxy groups. Ortho dihydric phenols give a green color, becoming violet and then red on adding sodium bicarbonate, meta compounds a deep violet, and the para a green, immediately changing to yellow due to the formation of quinone.

When the phenols are dissolved in concentrated sulphuric acid and treated with a nitroso compound or a nitrite, colored solutions result which after diluting and adding excess of alkali become blue or green. This is known as Liebermann's reaction.

The phenolic hydroxyl has certain acid properties, reacting with caustic alkalies to form salts stable in the presence of water, but decomposed by carbon dioxide and all other acids with regeneration of the phenols. Phenols can thus be removed from ethereal solution by caustic alkalies, and recovered by acidulating and shaking out with ether. They are not removed by carbonates or bicarbonates, and hence are readily separated from acids.

The metallic phenolates react with alkyl halides and acid chlorides to form substances analogous to the ethers and ethereal salts, the former being stable to alkalies, the latter undergoing hydrolysis.

With phosphorus halides, acetic anhydride and acetyl chloride, the phenols behave in the same way as the alcohols. On oxidation, however, they do not yield aldehydes or ketones.

Many of the phenols are of medicinal importance, others are of interest chiefly as they serve to identify certain drugs or essential oils, and still others important in being hydrolytic products of the decomposition of glucosides, and hence aid in the identification of the parent substance.

Phenol or Carbolic Acid, C_6H_5OH

Carbolic acid, or hydroxybenzene, is a powerful antiseptic and will often be found as one of the ingredients of a medicinal product. It is dispensed with petrolatum, and occurs in ointments combined with zinc oxide, menthol, turpentine, tannin, glycerin, and other antiseptic and astringent drugs. Some of the most widely advertised ointments and medicated soaps contain as the sole ingredient on which any claim of virtue can be claimed, a minute quantity of phenol or cresol.

Solutions of carbolic acid are used for aborting boils, carbuncles, and coldsores; for urethral injections and for spraying the throat and nose. It is also dispensed with iodin in admixture with glycerin and with sodium sulphoricinate.

The carbolates or phenates of sodium and potassium are antiseptics, soluble in water, and used internally in diarrhea, dysentery, and typhoid fever. Zinc phenate is only slightly soluble in water and is used as a dusting powder in surgery and skin diseases. Bismuth phenate is used as an intestinal antiseptic and for external purpose as an iodoform substitute.

The phenates of quinin and cocain are of commercial importance, the latter especially being employed in catarrhal conditions, alone and with acetanilid and menthol. A mixture of equal parts of camphor and carbolic acid is used in dyspepsia, flatulency, toothache, etc.

Pure carbolic acid forms beautiful snow-white crystals having a characteristic odor and a caustic action on the skin and flesh. When moist it forms a syrupy liquid, and as usually obtained in analytical work it remains in the liquid form. The crystals have a peculiar property of gradually turning red, the color appearing in that portion of the mass which is furthest from exposure to the air and extending to the surface.

The crystals melt at 40° C. and the liquid boils at 178–182° C. It is volatile at all temperatures. It is readily soluble in alcohol, ether, chloroform, glycerin, olive oil, and other organic liquids, and dissolves quite easily in water. It is practically insoluble in petroleum ether, but the absolute acid is miscible, being thrown out if a trace of moisture is present. It may be removed from acid solution with ether, and can be shaken out of ether or other organic solvents by sodium hydroxide, but not by carbonates. The alkaline phenolate solutions are decomposed by mineral acids. On account of the difference in the behavior of phenols and carboxy acids toward mild alkalies it is a simple matter to separate them by first dissolving in ether and chloroform, shaking out the acids with bicarbonate solution, and then removing the phenols by sodium hydroxide.

An aqueous solution of carbolic acid gives with bromin water a white precipitate which at first redissolves and then becomes permanent as more

of the reagent is added. It appears to be orange yellow when viewed in solution. This precipitate has the composition of tribromphenol bromide. On filtering and washing with dilute sulphite and then with water, tribromphenol is left, which has the composition $C_6H_2Br_3OH$, and which on drying over sulphuric acid melts 95° C.

When a dilute aqueous solution of carbolic acid is treated with a drop of dilute ferric chloride a violet blue color is obtained. If an aqueous solution is mixed with a little dilute ammonia water and treated with sodium hypochlorite solution a blue color develops.

Albumen and collodion solutions are coagulated by carbolic acid. Ortho and para nitrophenols are obtained by treating phenol with dilute nitric acid in the cold. The former can be separated from the latter by steam distillation. The meta compound is obtainable only indirectly. They melt respectively 45°, 96°, 114°.

Trinitrophenol or picric acid is obtained when phenol is dissolved in concentrated sulphuric acid and concentrated nitric acid gradually added. It forms brilliant yellow crystals melting 122.5° C. and is of medicinal importance.

When carbolic acid is fused with phthalic anhydride it gives phenolphthalein, which is recognized by the intense beet-red color imparted to an alkaline solution. The procedure which is also applicable to all phenols is as follows: Equal weights of the sample and reagent, amounting to .05 gram, are introduced into a dry test-tube, moistened with a drop of concentrated sulphuric acid and heated in an oil-bath at 160° for three minutes. The mixture is then cooled, 2 mils of water added and 1 to 2 mils of dilute sodium hydroxide.

Resorcin gives fluorescein, guaiacol gives a violet blue to violet color, orcin orange red.

When carbolic acid is dissolved in chloroform, a small piece of potassium hydroxide added and boiled, the liquid gradually assumes a pink color. Other phenols give more or less characteristic colors.

In the general scheme of qualitative analysis carbolic acid will appear as an oily residue on evaporating the ether shake-out from acid solution. If it is present in marked quantity its odor will distinguish it, and its presence can then be further substantiated by dissolving a small quantity in water and testing the solution with ferric chloride. The tribrom derivative should then be prepared and its melting-point determined and the phthalein fusion performed.

If the presence of carboxy acids is suspected the residue should be dissolved in ether and shaken with sodium bicarbonate solution in order to remove them. The phenol can then be shaken out with sodium hydroxide and recovered by adding excess of mineral acid and shaking out with ether.

When carbolic acid occurs in ointments or in oily mixtures, it can be

determined by dissolving a weighed portion in ether and extracting the solution three times with dilute sodium hydroxide. The alkaline solution is acidulated with hydrochloric acid and if a precipitate occurs due to fatty acids, the liquid is cooled, filtered, the filter washed with water, the acid liquid treated with an excess of bromin water, stoppered, and allowed to stand until the precipitate has agglomerated, when it is filtered onto a tared Gooch, washed with sulphite solution, and then several times with cold water. It is then dried over sulphuric acid and weighed.

Soaps should be dissolved in warm water and the solution precipitated with hydrochloric acid. When the fatty acids have separated, the mixture is poured onto a wet filter paper and the precipitate washed several times with water. The phenol which now is present in the filtrate and washings is ready for the bromin precipitation.

The pharmacopœial method for the evaluation of this substance is as follows:

Dissolve about 1.5 grams of the Phenol to be assayed, accurately weighed, in sufficient distilled water to make 1000 mils. Transfer an aliquot portion of this solution, containing not less than .038 gram not more than .041 gram of Phenol, to a 500-mil glass-stoppered flask having a long, narrow neck, add 30 mils of N/10 bromine V. S., then 5 mils of hydrochloric acid, and immediately insert the stopper. Shake the flask repeatedly during half an hour, allow it to stand for fifteen minutes, remove the stopper just sufficiently to introduce quickly 5 mils of an aqueous solution of potassium iodide (1 in 5), being careful that no bromin vapor escapes, and at once stopper the flask. Shake the latter thoroughly, remove the stopper and rinse it and the neck of the flask with a little distilled water, so that the washings may flow into the flask, then add 1 mil of chloroform, shake the mixture well and titrate with N/10 sodium thiosulphate V. S., using starch T. S. as indicator. It shows not less than 97 per cent of C_6H_5OH.

Each mil of N/10 bromin V. S. corresponds to .001568 gram of C_6H_5OH. Each gram of Phenol corresponds to not less than 618.6 mils of N/10 bromin V. S.

Trinitrophenol or Picric Acid, $C_6H_2(NO_2)_3OH$

This substance is almost universally known as picric acid, and is remarkable for its brilliant yellow color, which persists even in very dilute solutions. It melts 122.5°, soluble in alcohol, ether, chloroform, and to a moderate extent in water. It has strong acid properties, decomposing carbonates and forming explosive salts. The potassium salt is sparingly soluble in water, but the sodium compound dissolves with ease.

Picric acid gives precipitates with many of the alkaloids and an especi-

ally insoluble compound with antipyrin. It coagulates albumen and gelatin, and forms crystalline compounds with benzol, naphthalene, anthracene and many other hydrocarbons, so that it is sometimes used in detecting and purifying small quantities of these substances.

It is removed from its solution in mineral acids by immiscible solvents, and may be identified by the above-mentioned properties and by its dyeing of silk and wool, but not cotton. It can be titrated with alkali, using phenolphthalein as an indicator.

Picric acid is an antiseptic. The acid and its salts are used in malaria and trichiniasis; externally for burns, hemorrhage, erysipelas, eczema, etc., and as an injection for gonorrhea. Picric acid gauze is an important agent in surgical practice.

The silver compound is called Picratol, and is used as an antiseptic in gonorrhea and in catarrhal affections of the throat and nose.

Tribromphenol, $C_6H_2Br_3OH$

Tribromphenol or Bromal is a white to reddish crystalline powder with a bromin-like odor. It melts 95°, is insoluble in water, but dissolves in the ordinary organic solvents.

It is employed as an external and internal antiseptic. It is given in cases of typhoid fever, cholera infantum, etc., and externally is applied to wounds and running sores, and in the form of glycerin solution in diphtheria. It is often dispensed in an oily medicine or in the form of an ointment.

A product of somewhat uncertain composition, but claiming to be a bismuth tribromphenate is known as Xeroform. It contains 57 to 61 per cent Bi_2O_3, and is a yellow, neutral, insoluble powder possessing the combined virtues of bismuth and tribromphenol.

According to the patent it is obtained by dissolving tribromphenol in sodium hydroxide and adding bismuth nitrate to the sodium tribromphenolate solution. The precipitated tribromphenol bismuth is collected and washed with alcohol.

It is insoluble in water, alcohol, chloroform, liquid petrolatum, and vegetable oils, but soluble in 2 per cent hydrochloric acid in the proportion of 30 : 100. By alkalies it is decomposed with the formation of bromides; it is not decomposed by heat at temperatures below 120° C.

It should yield 59.5 per cent of bismuth oxide. If 1 gram is boiled with sodium hydroxide T. S. filtered, the filtrate rendered acid with sulphuric acid and the white, curdy precipitate washed and dried, it should melt at 95° C.

It is useful as an odorless and efficient substitute for iodoform in weeping eczemas; internally, in gastrointestinal catarrh, proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum, etc.

Paraiodophenol, $C_6H_4OH \cdot I$

Phenol iodide is a colorless or reddish crystalline substance melting about 92°, used as an antiseptic by itself or in glycerin admixture and is applied in diphtheria, cancer, leucorrhea, ringworm, and other diseases where a strong antiseptic is indicated.

Ethyl Carbolate, $C_6H_5OC_2H_5$

The ethyl ester of phenol known as Phenetol is an oily liquid, boiling 172°, soluble in alcohol and ether.

The Cresols, $C_6H_4OH \cdot CH_3$

The three isomeric cresols occur in coal tar and a purified mixture of the three compose the pharmacopœial product known as cresol or cresylic acid. It is used as a disinfectant and antiseptic either by itself or in admixture with soap. Large quantities of crude cresol are used in the manufacture of sheep and cattle dips. Household antiseptics of the creolin and lysol type contain essential quantities of neutralized cresols.

The cresols resemble carbolic acid in most of their properties; they form sodium and potassium cresylates, which are decomposed by carbon dioxide and by stronger mineral acids, so that on acidifying an alkaline solution they may be shaken out with ether. They yield alkyl derivatives by the displacement of the hydrogen in the hydroxyl group, and on distillation with zinc dust they are all converted into toluene. They give blue colors with ferric chloride.

Ortho cresol melts 31°, boils 188°; meta melts 5°, boils 201°; para melts 36°, boils 198°.

The presence of the hydroxyl group in the cresols protects the methyl group from the easy oxidation which characterizes the methyl group of toluene. However, if the hydrogen of the hydroxyl is replaced by a radicle, the protective influence is removed and substances like methyl cresol, $C_6H_4CH_3 \cdot OCH_3$, are readily oxidized to benzoic acid derivatives.

The cresols are soluble in water to some extent, and mix in all proportions with alcohol, ether, and petroleum ether, differing in this last respect from carbolic acid.

Estimation of Cresols or Cresylic Acid in Cattle Dips.—Chapin.—Fifty grams of coal-tar cresote or 15 to 20 grams of cresylic acid dip are weighed into a 500-mil round-bottomed flask, 20 mils of 1 : 3 H_2SO_4 are added, and the phenols are distilled off with steam. The flask will require no heating if a rapid current of steam is passed into it, but may with advantage be packed in cotton or felt. Obviously the apparatus must be so set up and the distillation so conducted that particles of resin may not be

mechanically carried over by the current of steam. Toward the end of the distillation any naphthalene in the condenser is melted out by shutting off the water for a few minutes, or if separated earlier in sufficient quantity to threaten stoppage of the condenser tube, distillation is interrupted while hot water is run through the condenser. The distillate is received in a liter flask approximately marked for each 100-mils capacity and joined to the condenser by a cork, which is pierced by a small glass tube connected to a small U-tube containing a little dilute caustic soda. The latter acts as a trap to prevent any loss of the distilled phenols. Distillation is continued untill 1 or 2 mils collected in a test tube gives no reaction with any appropriate reagent for phenols, such as ferric chloride. A volume of 800 mils is ample in nearly all cases.

A supply of benzol should be prepared by shaking a good grade of benzol with dilute sulphuric acid, then with dilute caustic soda two or three times, and then passing through a dry filter. A small wash bottle containing some of this benzol will be found very useful for rinsing the necks of separatory funnels, etc. Of this purified benzol 150 mils are measured out conveniently at hand, the contents of the U-tube and 5 mils of 1 : 1 H_2SO_4 are added to the distillate, and the latter is shaken up and poured into a separatory funnel of 1500 mils capacity, the flask being rinsed out with successive portions of the 150 mils benzol. When all is in the funnel 25 grams of clean sodium chloride is added for each 100 mils of distillate, and the funnel well shaken for five minutes and left at rest one-half hour. The aqueous layer is then run off slowly and completely, the funnel being allowed to stand until there is no further separation. The benzol solution of phenols and hydrocarbons is transferred to a 500-mil Erlenmeyer flask, while the aqueous portion is poured back into the separating funnel and extracted twice more in the same way, 100 mils of benzol being used each time. The funnel should always be gently handled after the aqueous portion has been drawn off, to prevent any impurities from the sodium chloride which have deposited upon its sides from becoming mixed with the benzol solution. The three benzol extracts are united in the Erlenmeyer flask, 15 mils of pure caustic soda solution, 1 : 2, is added, and the contents of the flask are subjected to a rotatory motion for some time in order that the phenols may be taken up by the caustic soda as completely as possible.

After the addition of a few grains of sand the flask is immersed in a water-bath, connected to a condenser, and all but 40 to 50 mils of the benzol distilled off. With the aid of a wash-bottle containing water and provided with a fine jet, only a small portion of water being used at a time, the contents of the flask are next carefully washed into a 150-mil separatory funnel. With proper manipulation the flask should be completely washed when the volume of aqueous portion in the separatory

funnel amounts to not more than 50 mils. Ten mils of strong sulphuric acid (100 mils pure concentrated H_2SO_4 to 120 mils water) is next slowly introduced with gentle rotation of the funnel, the addition of acid being interrupted and the funnel cooled whenever it becomes unpleasantly warm to the hand. Two or three drops of methyl orange are now added; and if on mixing the contents of the funnel the lower layer does not acquire a pink color, the addition of acid is continued until acidity is assured. Sufficient benzol is then added to make the two layers in the funnel approximately equal in volume, the funnel is thoroughly shaken, and with loosened stopper, left at rest for two hours. After that time the aqueous layer is slowly and completely run out, the analyst making sure that on longer standing no more will drain down from the sides of the funnel. The benzol solution of phenols is then ready to be transferred to the measuring tube.

The measuring tube consists of a glass-stoppered pear-shaped bulb of about 100 mils capacity, joined at its tapering end to a tube about 1 foot long and of a capacity of 25 to 30 mils. This tube is accurately graduated to contain 25 mils at 20° C. in divisions of one-tenth mil.

The apparatus is cleaned thoroughly with soap powder and hot water, and dried, best spontaneously, though alcohol and ether may be used if pure. Perfect cleanliness is essential to insure a properly shaped meniscus. Between 15 and 16 mils of caustic soda solution, 1 : 3, is brought into the tube with a pipette. The caustic soda should not be allowed to come in contact with the interior of the bulb or the upper part of the tube. After a few moments about 1 mil of benzol is added, and after waiting a little the height to the top of the now almost flat meniscus is noted. The benzol solution of phenols is next transferred from the separatory funnel to the tube, care being used to avoid mixing with the soda; the separatory funnel is washed out with a little benzol, which is also transferred to the tube, and the height of the meniscus is again noted. The latter may often be obtained more accurately at this point. The tube is then stoppered, vigorously shaken for three minutes, and set aside for at least three hours. An occasional rapid rotation of the tube between the palms of the hands will insure a complete separation of the layers. Each mil increase in volume of the caustic soda solution may be taken to represent one gram of phenols. All readings of the tube should be taken at the top of the meniscus and at a temperature as near 20° C. as practicable.

Europhen

Di-Isobutyl-Cresol Iodide,

$$C_6H_3(C_4H_9)(CH_3)(OI)\cdot C_6H_2(CH_3)(:O)(\cdot C_4H_9),$$

is a condensation product of 2 molecules of isobutylorthocresol, with 1 atom of iodin, analogous to thymol iodide.

It forms a yellow, voluminous powder, fusing at 110° C., containing 28 per cent of iodin, and having a faint saffron-like odor. It is insoluble in water or glycerin, but readily soluble in alcohol, ether, chloroform, and the fixed oils. It is permanent in the dry state, but splits off iodin readily when moistened and rapidly when heated with water at 70° C., particularly in the presence of alkalies.

When triturated with glycerin and water, it yields a filtrate which is turned bluish by the addition of freshly prepared starch paste. Its alcoholic solution produces a yellow precipitate with mercuric chloride.

Triiodometacresol or Losophan, $C_6HI_3OHCH_3$

Losophan is a colorless, crystalline body with a strong characteristic odor. It is insoluble in water and only slightly in alcohol, but dissolves in ether and chloroform and is used in alcoholic solution or in ointments for eczema, acute inflammation and parasitic skin diseases.

Cinnamylmetacresol or Hetacresol

This is a white crystalline powder, insoluble in water, but dissolving in ether, in which solution it is used as an antiseptic wash for sores, fistulas, and tubercular lesions.

The Cresalols

The cresylic esters of salicylic acid are called cresalols,

$$C_6H_4OHCOOC_6H_4CH_3.$$

They are all white crystalline powders soluble in alcohol and ether and insoluble in water, the ortho, melting 35°, is not of importance therapeutically; the meta, melting 74°, and the para, melting 39°, are used for the same purposes as salol.

Cresatin

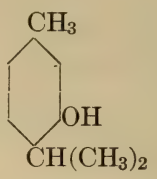
Meta-cresyl acetate is the acetic acid ester, $CH_3C_6H_4 \cdot O(CH_3CO)$, of meta-cresol, $CH_3C_6H_4 \cdot OH$.

Cresatin occurs as a colorless, oily liquid, possessing a characteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents, miscible with liquid petrolatum, fixed and volatile oils and is volatile with steam.

It is said to be useful in the treatment of affections of the nose, throat, and ear.

Thymol, $C_6H_4(CH_3)C_3H_7$

Thymol, which is isomeric with carvacrol, is a monohydroxy-derivative of cymene. Constitutionally it is



Thymol has attained considerable reputation as an antiseptic and anthelmintic. It is usually a component of mouth washes and gargles, and will often be found in tooth pastes and powders. It is used internally for rheumatism, gout, typhus fever, whooping cough, influenza, and gastric fermentation and as an expellant of the hook-worm. Its presence may be suspected in remedies intended for any of the above diseases.

The various combinations of mouth washes and gargles are too numerous to describe, but any of the listerine type or the glycothymoline type will probably contain thymol. One type of " shot gun " formula recommended as an astringent and antiseptic for leucorrhea contains thymol, eucalyptol, tannic, salicylic and boric acids, alum, and the extracts of Hyoscyamus, opium, helonias, and witch hazel, sold in tablet form. Nasal tablets contain thymol, menthol, eucalyptol, methyl salicylate, and the bicarbonate, borate, chloride, benzoate, and salicylate of sodium.

Thymol occurs in the volatile oil of Thymus vulgaris the common or garden thyme, in the volatile oils of Monarda punctata, Morula japonica, Cunila mariana, and Carum ajowan.

Thymol forms colorless transparent crystals, with a characteristic thyme-like, pleasant odor, melting 50–51° and boiling 220–322°. It dissolves but slightly in water, but is readily soluble in alcohol, ether, chloroform, petroleum ether, glacial acetic acid and the fixed oils. It forms soluble salts with alkalies. When triturated with camphor, menthol or chloral hydrate, a liquid is produced. It gradually volatilizes at the temperature of the water-bath.

An aqueous solution of thymol does not give a blue color with ferric chloride, but a concentrated solution in alcohol gives a transient blue color with a trace of the very dilute reagent. If a small crystal is dissolved in 1 mil of glacial acetic acid and treated with 6 drops of concentrated sulphuric acid and 1 of nitric acid, a deep bluish-green color will appear.

A solution of thymol in sodium hydroxide when agitated with chloroform develops a violet color.

A very characteristic test for thymol consists in dissolving a suspected residue in a small quantity of sodium hydroxide solution and adding slight excess of a solution of iodin in potassium iodide, when a brilliant red precipitate of di-thymol diiodide will gradually settle out. This substance is insoluble in water but dissolves in ether. It has the composition $C_{20}H_{24}O_2I_2$.

If 1 gram of thymol is dissolved in 1 mil of concentrated sulphuric acid, added to a mixture of 1 mil each of nitric acid and sulphuric acid and subjected to the temperature of a boiling water-bath for three to four minutes, trinitro thymol is formed, which may be obtained in a pure condition by pouring the mixture into 20 mils of cold water, cooling, shaking, filtering, washing, and then recrystallizing from a mixture of 10 mils water, 4 mils alcohol and .5 mil concentrated hydrochloric acid. It melts 109 to 110°.

When fused with phthalic anhydride the product has a violet-red to red color, which dissolves in sodium hydroxide with an intense blue.

When it is desired to determine thymol in admixture with other antiseptic agents such as are usually found in dentifrices, douches, etc., a measured quantity of the sample is introduced into a distilling flask arranged for steam distillation, with an outlet tube in the form of a spray trap such as is used in running Kjeldahl distillations. The material is diluted with water, acidulated with phosphoric acid, and distilled with the aid of a current of steam. The distillate is recovered in a flask closed as tightly as possible and surrounded with cold water. The amount of liquid to be collected depends on the nature of the sample, but it is well to continue the operation for half or three-quarters of an hour. The distillate is tested for acidity and if the reaction is acid a slight excess of sodium bicarbonate is added. It is then transferred to a separator and shaken out two or three times with ether, the ether extracts united, shaken with dilute caustic alkali, the alkaline solution transferred to a distilling apparatus of the type above described, acidulated with phosphoric acid and the thymol distilled off, collecting the distillate in a glass-stoppered flask. The estimation of the thymol in the distillate then follows the procedure of Seidell.[1] One mil of carbon tetrachloride is added and then bromin vapor poured in, a little at a time with alternate shaking and addition of bromin until the mixture retains a distinct brown color. After allowing to stand in a dark place for one-half hour, 5 mils carbon sulphide followed by 5 mils of 20 per cent potassium iodide solution are added, the bottle well shaken, N/10 thiosulphate run in until the pink color in the carbon bisulphide layer is just discharged, an additional amount of potassium iodide added, when if no further liberation of iodin occurs, the reading of the burette is taken. Five mils of 20 per cent potas-

[1] Amer. Chem. Journal, 47, 508.

sium iodate solution are added, the flask well shaken, and titration with thiosulphate continued until the iodin color is discharged a second time. The completion of the reaction may be tested by a further addition of iodide and iodate solutions. The difference between the first reading and the second corresponds to the hydrobromic acid formed by the action of the bromin on the thymol. The calculation is made on the basis of 2 molecules of hydrobromic acid to one of thymol. One mil N/10 thiosulphate is therefore equivalent to .0075056 gram of thymol.

Assay of Thymol.—The weighed sample of .1 to .5 gram of thymol is placed in a 300-mil stoppered bottle with 1 to 2 mils of carbon tetrachloride and 100 mils of water. Bromin vapor is then poured into the mixture till there is considerable excess after shaking. After half an hour, 5 mils of carbon bisulphide and 5 mils of 20 per cent potassium iodide solution are added, and the free iodin is titrated by means of N/10 thiosulphide solution. After adding a little more iodide, no further liberation of iodin should take place. Five mils of 2 per cent potassium iodate solution are then added, and the free iodin again titrated. The result is calculated as above described.

Dithymol diiodide, $(C_6H_2CH_3OIC_3H_7)_2$

This substance which we will call simply thymol iodide, is extensively used as a substitute for iodoform in antiseptic dusting powders, medicated gauzes, and bandages. It is sold under a number of different names including aristol, thymoto, iodistol, iodohydromol, iodothymol, iodosol, iosol, iothymol, thymiode, thymodin, etc.

Thymol iodide is a bright-red or pinkish red powder with a slight odor and a chalky feel. It is insoluble in water and only slightly in alcohol, but dissolves readily in ether, chloroform, and oils. On exposure to light it is gradually decomposed.

U. S. P. Method of Assay.—Mix thoroughly about .25 gram of Thymol Iodide, previously dried to constant weight in a desiccator over sulphuric acid and accurately weighed, with about 3 grams of anhydrous sodium carbonate. Cover the mixture with about 1 gram more of anhydrous sodium carbonate and heat it moderately, in a crucible, gradually increasing the heat, but not exceeding a dull redness, until the mass is completely carbonized. When sufficiently cooled, extract the residue with boiling distilled water and wash it on a filter with boiling distilled water until the washing ceases to produce an opalescence with silver nitrate T. S. Heat the combined washings, which measure about 150 mils on a water-bath and add an aqueous solution of potassium pemanganate (1 in 20) in small portions, until the hot liquid remains permanently pink. Then add just enough alcohol to remove the pink tint, cool the liquid to room

temperature, and dilute it to 200 mils. Mix it well and then filter through a dry filter, rejecting the first 50 mils of filtrate. To 100 mils of the subsequent clear filtrate add about 1 gram of potassium iodide (free from iodate) and an excess of diluted sulphuric acid, and titrate the liberated iodin with N/10 sodium thiosulphate V. S., adding starch T. S. near the end of the titration. It shows in the dried Thymol Iodide, not less than 43 per cent of I.

Each mil of the N/10 sodium thiosulphate V. S. used corresponds to .002115 gram of I. Each gram of Thymol Iodide corresponds to not less than 203.3 mils of N/10 sodium thiosulphate V. S.

Thymol Salicylate, $C_{10}H_{13}OC_7H_5O_3$

Thymol salicylate or salithymol is the reaction product of sodium salicylate with sodium thymolate and phosphorus tri-chloride. It is a white crystalline powder, soluble in alcohol and ether and slightly in water, used as an antiseptic.

Thymol Carbonate

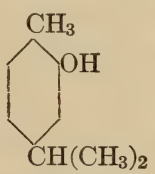
Thymol carbonate, thymotol, or tyratol is a derivative of thymol obtained by passing phosgene gas into a solution of sodium thymolate. It forms colorless crystals with a faint odor of thymol, soluble in alcohol, ether, and chloroform and insoluble in water. It is used as a vermifuge.

Thymoform

Thymoform is a condensation product of thymol and formaldehyde, soluble in alcohol, ether, chloroform, and oils, insoluble in water, and used as a substitute for iodoform.

Carvacrol

Carvacrol has the constitution



showing its close relationship to thymol. It is a liquid of specific gravity .981 at 15 °C., melting +.5° C., boiling 236–137° C., its alcoholic solution giving a green color with ferric chloride. In odor and general characteristics it is very similar to thymol. In concentrated solution with alcohol

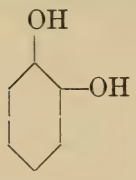
it gives a transient dirty-green color with a small quantity of dilute ferric chloride.

This phenol often accompanies thymol in oil of thyme from certain sources, in fact sometimes replaces its isomer entirely. Its chief sources, however, are the oils of several species of Origanum. The oil of O. vulgare, Wild Marjoram, is used as an antiseptic and emmenagogue, and in the trade the oil commonly called " oil origanum " is really thyme oil.

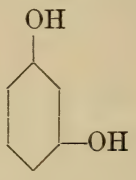
Cretan origanum oil, of which there are two varieties, the Triest and Smyrna oil, has no special interest to the drug chemist.

Dihydric Phenols

The dihydric phenols and their derivatives furnish a number of interesting and important medicinal bodies. The relationship of the three isomeric dihydric phenols is apparent from the following formulæ:



Catechol or Ortho-dihydroxy-benzene



Resorcinol or Meta-dihydroxy-benzene

Hydroquinone or Para-dihydroxy-benzene

Catechol, $C_6H_4(OH)_2$

Catechol or pyrocatechin is widely distributed in nature, being associated with the tannins occurring in a great variety of plants, these particular tannins giving a greenish-black or greenish-brown color with ferric chloride. It is present in catechu or cutch, an extract prepared from the wood of Acacia catechu, and is used as an astrigent.

Catechol is a colorless crystalline substance, melting 104° C., readily soluble in water, alcohol, and ether. Its aqueous solution gives a green color with ferric chloride, changing to violet and red on the addition of sodium bicarbonate and being restored to green on the cautious addition of sodium hydroxide. It reduces alkaline copper sulphate and silver nitrate in the cold, and gives a precipitate with lead acetate. In presence of alkalies it absorbs oxygen from the air, becoming brown and black; lime water causes a reddish or brown color. Pine wood moistened with hydrochloric acid is colored blue by a solution of catechol.

Catechol is an antiseptic and antipyretic and is used externally in solutions and ointments for burns, wounds, etc.

Aqueous solutions of catechol are neutral, but on adding borax the liquid acquires acid properties and decomposes carbonates. Pyrogallol and gallates of the alkalies act in the same way, but resorcinol, hydroquinone, and orcinol do not.

When the phthalein fusion test is applied, the melt gives a blue color with alkali.

Catechol is used to a limited extent as a remedial agent, but several of its derivatives are of marked importance. The monomethyl ester is well known as guaiacol, the dimethyl ester as veratrole, the monoethyl ester as guaethol, and the methyl benzyl ester as brenzcain. The sodium salt of its acetate, $C_6H_4OH \cdot OCH_2COONa$, is called guaiacetin, and is used in tuberculosis.

The tetrabrom-compound, useful for identification, may be prepared by dissolving .5 gram of catechol in 2.5 mils chloroform and adding .4 mil bromin. The solvent is evaporated, the residue dissolved in 5 mils cold alcohol, 20 mils water added, shaken, filtered, washed with 5 mils water and the procedure repeated. The resulting product after drying on a tile will soften at about 185–187°, melting 192–193°.

Guaiacol or Methyl catechol, $C_6H_4(OH)OCH_3$

Guaiacol is an important constituent of beechwood creosote, and is present in the distillate of other woods as well. Considerable quantities are obtained on distilling the heart wood of Guaiacum officinale, Lignum Vitæ.

Pure guaiacol is a faintly yellowish, limpid oily liquid with a characteristic aromatic odor. Its specific gravity is 1.110 to 1.220 at 15° C., and it boils 201 to 207° C., readily soluble in alcohol, ether, glycerin, glacial acetic acid, and fairly soluble in water. Its aqueous solution gives an emerald-green color with ferric chloride. It acts as a reducing agent in alkaline solution.

Guaiacol when heated with hydriodic acid yields methyl iodide and catechol. It has the properties of a weak acid, and its salts are decomposed by mineral acids. When potassium guaiacol is heated with methyl iodide, it yields methyl guaiacol, $C_6H_4(OCH_3)_2$, known as veratrol. Veratrol is an aromatic liquid which is also obtained by heating veratric acid with barium oxide.

If .1 gram of guaiacol in 1 mil of water is treated with .2 gram of picric acid in 5 mils of hot water, shaken and cooled slowly, orange crystals are obtained which when separated and washed will melt at 86° C.

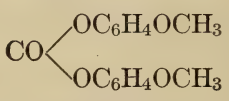
The chief use of guaiacol is in remedies for tuberculosis and pneumonia. It has antiseptic and antipyretic properties also, but its use for these purposes is limited. It is dispensed in capsules and pills and mixed with

wine and other alcoholic solutions. When used locally it is combined with fixed oils and glycerin. It is often combined with hypophosphites in elixirs and tablets, and may be anticipated in any proprietary remedy advertised for tubercular conditions, malt extract, and cod liver compounds especially. Beechwood creosote has perhaps a more general use than pure guaiacol, but as this creosote, when medicinally pure, consists of about 90 per cent of guaiacol, the chemistry of the two may be considered simultaneously.

Beechwood creosote, and for all intents and purposes guaiacol, will be found combined with bismuth subnitrate in tablets, with cerium oxalate, Nux Vomica and pepsin, with extracts of Podophyllum, Leptandra, Euonymus, and chirata as an intestinal tonic; with cod liver or olive oils in tonic capsules, with oil of santal and eucalyptus; and with iodoform, eucalyptol, and other antiseptics in oily inhalants.

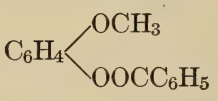
Guaiacol has been an attractive body for the chemical manufacturer to manipulate and exploit in various combinations. One of these derivatives, the carbonate, is official in our Pharmacopœia.

Guaiacol Carbonate



The name Duotol is also applied to this substance, which is a white crystalline, odorless, tasteless powder obtained by the action of carbonyl chloride on sodium guaiacol. It is insoluble in water, slightly soluble in glycerin and fixed oils, but dissolves readily in alcohol, ether, and chloroform. It melts 84 to 87°. It is saponified by alcoholic potash, and on acidulating the guaiacol is freed and may be recovered by shaking with ether. An alcoholic solution does not give a bluish-green color with ferric chloride.

Guaiacol Benzoate



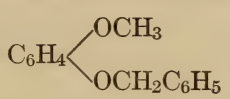
Benzoyl guaiacol or Benzosol is prepared by warming the potassium salt of guaiacol with benzoyl chloride and crystallizing the product from hot alcohol.

It forms colorless, minute crystals which melt at 59 to 61° C.; they are odorless and tasteless or nearly so. It is practically insoluble in water, sparingly soluble in ether, but readily soluble in hot alcohol. It contains 54 per cent of guaiacol.

It forms with sulphuric acid a permanent yellow coloration which on the addition of acetone assumes a characteristic, brilliant cherry-red color, distinguishing it from salol, which gives a yellow color. Ferric chloride produces in the benzosol sulphuric acid mixture a violet color, changing to green and blue, and on the further addition of nitric acid, to orange and green, or of potassium nitrate to green, violet, and yellow. When heated with alcoholic potash, the odor of guaiacol is developed.

Its uses are analogous to those of creosote and of benzoic acid. It is said to be useful in incipient pulmonary tuberculosis, as an intestinal antiseptic in fermentation, diarrhea, typhoid fever, diabetes mellitus, and as a urinary disinfectant in cystitis, etc.

Guaiacolbenzyl-ester or Brenzcain,



Brenzcain is used as a local anesthetic. It forms colorless crystals, melting at 62° C., soluble in alcohol, ether, and fixed oils. Its properties in comparison with the other local anesthetics have already been discussed in the chapter on Cocain.

Guaiacol Camphorate, $C_8H_{14}(COOC_6H_4OCH_3)_2$

This body, also called Guacamphol, is employed in certain conditions of phthisis, and is crystalline, insoluble in water, but soluble in alcohol and chloroform.

Guaiacol Cinnamate or Styracol

Styracol is guaiacyl cinnamate, $C_6H_5CH : CH \cdot CO \cdot O \cdot (C_6H_4 \cdot OCH_3)$, the cinnamic acid ester of guaiacol.

It forms colorless, odorless, and tasteless crystalline needles, melting at 130° C. It is insoluble in water, but easily soluble in alcohol, acetone, chloroform, and benzine. It contains 55 per cent of guaiacol, which is split off by the action of alkalies.

Styracol is an intestinal antiseptic. It is useful in the initial stage of tuberculosis, in chronic enteritis, and in intestinal disturbances in general, catarrh of the bladder, etc.

Guaiacol Glycerylether or Guaiamar

Guaiamar is glyceryl guaiacolate,

$$CH_3O \cdot C_6H_4 \cdot O(CH_2OH \cdot CHOH \cdot CH_2).$$

It is a white, crystalline, non-hygroscopic powder, melting at 75° C. and having a bitter, aromatic taste. It is soluble in 20 parts of water at the ordinary temperature, but dissolves best in warm water; it is soluble in alcohol, chloroform, ether, and glycerin. Its solutions are neutral to test paper. It is decomposed by soluble hydroxides and carbonates and by strong acids.

It is intended to be used as a substitute for guaiacol in cases in which the latter is indicated. In the form of ointment it has been recommended in acute articular rheumatism.

Guaiacol Phosphate, $(C_6H_4 \cdot OCH_3 \cdot O)_3PO$

Guaiacol phosphate is a white crystalline powder, melting 98°, insoluble in water and ether, but dissolving in alcohol and chloroform.

Guaiacol Phosphite, $(C_6H_4OCH_3 \cdot O)_3P$

Guaiacol phosphite melts 77–78° C., and is soluble in water and the organic solvents.

Guaiacol Salicylate

Guaiacol-salol is guaiacol salicylate, $C_6H_4 \cdot OH \cdot CO \cdot O \cdot (C_6H_4 \cdot OCH_3)$, the salicylic acid ester of guaiacol, closely related to phenyl salicylate (salol).

It is a white crystalline powder, tasteless, but having a salol-like odor. It is insoluble in water, but soluble in alcohol, ether and chloroform. It melts at 65° C.

It is decomposed by alkalies and alkaline carbonates with the formation of alkali salicylate and alkali guaiacol. The alcoholic solution is colored wine red by the addition of ferric chloride, but if the alcoholic solution is dropped into a watery solution of ferric chloride a turbidity but no coloration is produced.

Guaiacol Valerate, $C_6H_4 \cdot OCH_3 \cdot OCOC_4H_9$

Geosote is a colorless or yellowish liquid boiling 265° C.

Guaiacol Methyl Glycolate—Monotal

Monotal is $CH_2(O \cdot CH_3) \cdot COO \cdot (C_6H_4 \cdot OCH_3)$, the methyl-glycolic acid ester of guaiacol.

It occurs as a limpid, colorless oil, of a faintly aromatic odor, easily soluble in alcohol, ether, benzol, and chloroform; difficultly soluble in water. It is soluble in about 6 parts of olive oil. It boils under 15 mm.

pressure at about 156° C. It is split up into guaiacol and methylglycolic acid when treated with caustic alkalies.

Monotal is easily saponified by aqueous or alcoholic solutions of potassium hydroxide and then gives the reactions characteristic of guaiacol and methylglycolic acid. It has a specific gravity of 1.17 to 1.18 at 20° C.

It is used as an analgesic.

Potassium Guaiacol Sulphonate. Thiocol

Thiocol is potassium guaiacol sulphonate, $C_6H_3(OH)(OCH_3)(KSO_3)$ 1 : 2 : 6.

It is a colorless, crystalline powder, neutral or faintly alkaline, odorless, and having a faint bitter, followed by a sweet taste. It is readily soluble in water, slightly soluble in ordinary alcohol, but insoluble in absolute alcohol and in ether or oils. Its aqueous solution is not precipitated by barium chloride; ferric chloride produces an intense violet-blue color, which disappears on the addition of ammonia, or of concentrated solution of alkali chlorides or sulphates.

It is used in pulmonary tuberculosis, acute and chronic bronchitis, pneumonia, whooping cough, etc.

Calcium Guaiacolmonosulphonate, $Ca(C_6H_3OH \cdot OCH_3SO_3)_2$

This salt, also known as guaiacyl, is a bluish-gray powder soluble in water and alcohol and used as an anesthetic.

Methylene diguaiacol or geoform is a condensation product of formaldehyde and guaiacol, and has been described in the chapter on "Aldehydes." An acetylated compound of geoform is called Euguform.

Among the compounds of guaiacol and the alkaloids may be mentioned piperidin guaiacolate or guaiaperol, melting 80° C., soluble in water, alcohol, and ether; quinin guaiacol bisulphonate or guaiaquin and quinin dihydrobromguaiacolate or guaiaquinol.

Silver eosolate is the silver salt of trisulphoacetylguaiacol,

$$C_6HO \cdot CH_3 \cdot OC_2H_3O \cdot Ag_3(SO_3)_3,$$

an antiseptic substance used in gonorrhea, in the form of an injection or in bougies.

Calcium eosolate, the calcium salt of the same acid,

$$Ca_3(C_6HO \cdot CH_3OC_2H_3O(SO_3)_3)_2,$$

is soluble in water and acids, and slightly in alcohol.

Histosan is a guaiacol-albumin compound soluble in alkaline liquids.

Creosote Carbonate—Creosotal

Creosote carbonate is a mixture of carbonic acid esters, analogous to guaiacol carbonate, prepared from creosote.

It is a yellowish, thick, honey-like, perfectly clear and transparent liquid, containing 92 per cent of creosote. It is odorless and has a bland oily taste. It is insoluble in water, but soluble in alcohol, ether, chloroform, benzene, and in fixed oils.

The addition of a few drops of ferric chloride solution to the alcoholic solution should not cause any change in color. On boiling with potassium hydroxide solution the odor of creosote is evolved.

Creosote carbonate has the same action as creosote, but is claimed to be non-toxic and devoid of irritant properties. It is recommended as a substitute for creosote for internal exhibition in tuberculosis, pneumonia, and as an intestinal antiseptic.

Creosote phosphate is analogous to guaiacol phosphate, insoluble in water and alkalies.

Creosote phosphite is called Phosphotal, is soluble in alcohol, water, and ether.

Creosote tannate or Tanosal is an astringent antiseptic used for throat and bronchial troubles, soluble in water, alcohol, and glycerin, and insoluble in ether.

Creosote valerate or Eosote is a colorless or yellowish liquid soluble in alcohol and ether.

Creosote oleate is a yellowish oily liquid soluble in alcohol, ether, and chloroform.

Methylenecreosote or Pneumin is a condensation product of creosote and formaldehyde.

Creosote

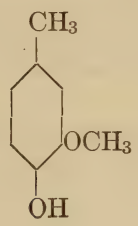
The creosote used for medicinal purposes is a mixture of phenols and phenol derivatives, which according to the Pharmacopœia should be chiefly guaiacol and creosol, obtained by purifying a distillate of wood tar, chiefly that obtained from birch wood. It is a colorless or yellowish, highly refractive liquid with a smoky odor, soluble in alcohol, ether, chloroform, fixed and volatile oils, and miscible with considerable water to a cloudy liquid. Its saturated aqueous solution gives a transient violet-blue color, which soon changes to greenish and brown, with a brown precipitate. It gives a reddish precipitate with bromin water.

It is generally reported by investigators that creosote varies greatly in composition.

Coal-tar creosote commonly consists of that portion of coal tar which distills between 200 to 300° together with the residual oils from the manu-

facture of crude carbolic acid, naphthalene, and anthracene. It usually contains naphthalene, phenanthrene, anthracene, diphenyl, and other solid hydrocarbons, carbolic acid, cresols and other phenols, pyridine and other basic substances, and so-called undetermined indifferent oils. Hager's test for the detection of coal-tar products in wood creosote is as follows: One volume of the sample is agitated in a Mohr's burette with 3 volumes of diluted glycerol (1 vol. water to 3 vols. absolute glycerol) and the mixture allowed to stand until separation has occurred. If the creosote is pure the volume will remain unchanged. If reduced the glycerol layer is withdrawn and the treatment repeated and the volume again observed, the residual layer indicating the proportion of real wood creosote in the sample taken. The coal-tar products can be detected in the first glycerol fraction by filtering, diluting with water, and agitating the chloroform. On allowing the separated solvent to evaporate spontaneously, the residue should be tested by shaking a portion with half its volume of an ethereal solution of collodion when, in the presence of much carbolic acid, the collodion will coagulate to a transparent jelly. If a drop of the residue is treated with a few drops of neutral ferric chloride in a small porcelain evaporating dish the reagent will assume a fine violet coloration.

Homocatechol Methyl Ester or Creosol

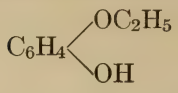


Creosol is homologous with guaiacol and occurs in that fraction of creosote boiling about 220° C. It is colorless when freshly distilled and has a vanilla-like odor. It is soluble in alkalies and a solution in strong alcoholic potash sets to a mass of needles of the potassium compound. It reduces silver nitrate on warming and gives a green color with ferric chloride.

Dimethyl Homocatechol, $C_6H_3 \cdot CH_3(OCH_3)_2$

This body also occurs in beechwood creosote. It gives no color with ferric chloride and is insoluble in aqueous solutions of alkali hydroxides.

Catechol Monoethyl Ester



This substance is closely related to guaiacol and is called Guaethol and also, though illogically, guaiacol ethyl. The last term is erroneous and confusing because it is not ethyl guaiacol.

It is a colorless crystalline mass melting at 27 to 28° C., or an oily almond-colored liquid, with a pleasant aromatic odor. It boils at about 215° C., dissolves in alcohol, ether, and chloroform, but is insoluble in water.

It is used for the same purposes as guaiacol.

Resorcinol

Resorcinol or meta-dihydroxybenzol has been recommended for a number of ailments, but its largest use is probably for aiding the removal of dandruff, and hence its presence may be expected in hair tonics and other mixtures designed to improve the condition of the scalp. Hair tonics may contain in addition to resorcinol, quinin, cantharides, extract of sage, precipitated sulphur, lead acetate, beta-naphthol, glycerin, and alcohol.

Resorcinol is also used internally for asthma, hay fever, seasickness, whooping cough, diphtheria, etc., where remedies of an antiseptic, antipyretic, or antizymotic action are indicated. It is also applied in inflammatory conditions of the mucous membrane of all parts of the body, and in erysipelas.

It will be found in tablets with sodium bicarbonate and borax, and in ointments combined with other antiseptic agents.

When pure, resorcin is a white crystalline substance, but on standing and especially on exposure to the light, it turns reddish. It melts 109–111°, dissolves easily in water, alcohol, and ether, slightly in chloroform, benzol, and carbon bisulphide. Its aqueous solution gives a dark-violet color with ferric chloride, and a crystalline precipitate of tribromresorcinol with bromin water, but no precipitate is given by lead acetate. It reduces ammoniacal copper and silver salts. When fused with phthalic anhydride the melt dissolves in sodium hydroxide with a beautiful green fluorescence due to the formation of a fluorescein. This reaction is characteristic of other meta-dihydric phenols.

The trinitro-compound prepared as described under Thymol melts 175°; .1 gram resorcinol when boiled with 1 mil of potassium hydroxide to which a drop of chloroform is added develops a crimson color.

A solution of resorcinol mixed with copper sulphate and sufficient

ammonia to redissolve the precipitate first produced, yields a deep black liquid which dyes wool and silk black.

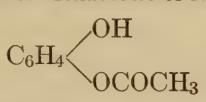
Resorcinol may be shaken out of its solution in ether by using dilute alkali, and on acidulating the latter, the resorcinol may be recovered by ether. In the general scheme of analysis it will appear when a residue left by shaking the aqueous acid solution with ether, is examined and it may be identified by applying the reactions above described.

C. M. Pence [1] has made a study of the methods of estimating resorcinol, and recommends the following for assaying the commercial article: 1.4563 grams of the sample are dissolved in water and made up to 500 mils in a graduated flask. A 25-mil portion is transferred to a 500-mil glass-stoppered flask, 50 mils N/10 bromin added, 50 mils water and 5 mils concentrated hydrochloric acid, the mixture shaken and allowed to stand for one minute; 200 mils of water are then added, 5 mils of 20 per cent potassium iodide and after five minutes the liberated iodin is titrated with sodium thiosulphate. The number of mils of N/10 bromin solution consumed divided by .4 gives the percentage of resorcinol. A blank is run using 7 to 10 mils of potassium iodide.

A mixture obtained by melting together equal parts of resorcin and iodoform is sold under the name of "Resorcinol." It is an amorphous brown powder, with an iodin odor, and is used as an antiseptic in ointments and dusting powders.

Potassium diiodoresorcinol monosulphonate, $C_6HI_2(SO_3K)(OH)_2$, is used as an antiseptic under the name "Picrol."

Resorcinol Monacetate or Euresol



Euresol is a thick, yellowish, oily liquid with an agreeable odor, boiling 283° C. It is soluble in acetone and in alkaline solutions, and is used in the treatment of chilblains, acne and as a substitute for resorcin in external application.

Fluorescein

Resorcinolphthalein—$O : (C_6H_3OH)_2 : C \cdot C_6H_4 \cdot COO$.

Fluorescein is prepared by the fusion of phthalic anhydride and resorcinol at 195 to 200° C. till the mass becomes solid. This is extracted with water and the residue dissolved in potassium hydroxide solution, which is then filtered and the fluorescein precipitated with acid.

It is an orange red powder, insoluble in water, ether, chloroform, and benzol; soluble in hot glacial acetic acid and boiling alcohol. It dissolves in alkaline solutions with formation of salts.

[1] J. Ind. and Eng. Chem., 1911, 3, 820.

The alkaline solution by transmitted light is red; by reflected light it has a green flourescence even in very dilute solutions. When fluorescein is boiled with chalk water, the calcium salt of fluorescein is formed which is recognized by its red-brown color and green sheen.

The soluble sodium salt of fluorescein has been used for the diagnosis of corneal lesions and detection of minute foreign bodies imbedded in the cornea.

Resorcinol-salol and resorcinol-eucalyptol are antiseptics. Resorcinol-hexamethylenetetramine or Hetralin is used in gonorrhea and cystitis.

Resorcinol is combined with mercury in a substance called mercury-resorcinol acetate, a yellow crystalline powder, soluble in alkalies and strong acids, and used as a hypodermic in syphilis, and in ointment form for local application.

Resaldol

Resaldol is the acetyl derivative of a condensation product of chlormethylsalicylic aldehyde and resorcin. It is a yellow, amorphous, light powder insoluble in water, but soluble in alkalies. It is used as an intestinal antiseptic.

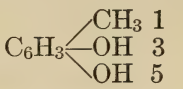
Hydroquinone

Hydroquinone, though used to a slight extent as an antiseptic and antipyretic, is best known as a photographic developing agent. Its most important feature in connection with drug chemistry is its relation to the glucosides and its appearance as a product of the hydrolysis of these principles. It is one of the products of the hydrolysis of arbutin.

It forms colorless crystals, melting 169° C., dissolving easily in alcohol and ether and less readily in water. When its aqueous solution is treated with ferric chloride, fine green metallic crystals of quinhydrone, $C_6H_4O_2 \cdot C_6H_4(OH)_2$, appear, which can be crystallized pure out of boiling water. This substance dissolves in alcohol and ether to a yellow-colored solution and in ammonia to a green, which turns brown on exposure to the air.

Hydroquinone-dimethyl ester, melting 56° C., is formed by boiling hydroquinone under pressure with methyl iodide and potassium hydroxide.

Dihydroxytoluol or Orcinol



Orcinol occurs in many lichens, probably combined in complex acid or glucosidic combinations, and is freed on hydrolysis. It has been

obtained from some of the well-known vegetable colors, litmus, cudbear, and archil, and recovered from the alkaline fusion of aloes. It has a limited use as an antiseptic in skin diseases. Orcinol forms colorless crystals containing 1 molecule of water, which redden on exposure. It has a sweet but unpleasant taste. The crystals melt at 58-59° C., and lose all the water of crystallization below 100°. It dissolves readily in water, alcohol, and ether and the aqueous solution gives a violet color with ferric chloride.

It forms a crystalline compound with ammonia, and when its ammoniacal solution is exposed to the air it absorbs oxygen, giving a purple solution from which acetic acid precipitates a red coloring matter called orcein. The new substance is sparingly soluble in water unless alkaline, but dissolves in alcohol to a purple solution which is turned red by acid.

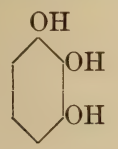
Maltol, $C_6H_4O(OH)_2$

Maltol is a phenolic body which occurs naturally and which was for a long time confused with salicylic acid in testing for preservatives in malt liquors. It is difficultly soluble in cold water and benzol, but dissolves easily in hot water, ether and alkalies, and is precipitated from the latter by carbon dioxide. Its aqueous solution gives a violet color with ferric chloride, reduces Fehling's solution and ammoniacal silver oxide. It does not, however, respond to test of Jorissen for salicylic acid, by which a red color is developed in the presence of this acid when 4 to 5 drops of 10 per cent potassium nitrite, 4 to 5 drops 50 per cent acetic acid and 1 drop of 10 per cent copper sulphate are added and shaken with the suspected sample.

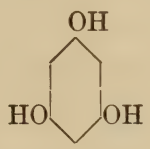
Maltol appears to be a reaction product resulting from the caramelization of carbohydrates.

Trihydric Phenols

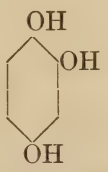
The type compound of this group exists in three isomeric forms, all of which are well known bodies:



Pyrogallol



Phloroglucinol



Hydroxyhydroquinone

Pyrogallol

Pyrogallol, called pyrogallic acid by the photographers, is used as an antiseptic in skin diseases. It may be obtained by heating gallic acid

with $2\frac{1}{2}$ parts of water to 210° in an autoclave, or with glycerin to 195° until the evolution of carbon dioxide ceases.

It crystallizes in fine needles, melting 132° C., boiling 210°, very soluble in water, alcohol, and ether, and turning brown and black in presence of alkaline solutions due to the rapid absorption of oxygen. Its aqueous solution gives with ferric chloride a red, and with ferrous sulphate containing a trace of ferric chloride a deep-blue solution.

Pyrogallol has powerful reducing properties, precipitating silver and gold in the metallic state, and therefore being of value in photography, and as a hair dye. When heated with phthalic anhydride it yields gallein, which is used as a red dye, the alkaline solution being rose-red. (Blue, Allen.)

When acetylated it yields triacetylpyrogallol, a substance known as Lenigallol, melting 165° C., insoluble in water, and dissolving in alkalies with decomposition. Lenigallol is used in psoriasis, eczema, and other skin diseases.

A monoacetate is marketed as Eugallol. Both of these may be saponified by alkalies, setting free pyrogallol, which of course is soon oxidized.

Saligallol is said to be pyrogallol disalicylate. It is marketed in acetone solution.

An oxidized pyrogallol is sold as a remedy for skin diseases.

Phloroglucinol

Phloroglucinol is intimately associated with the chemistry of some of the glucosides and resins. It results from the hydrolysis of phloridzin, a glucoside of the bark of the apple tree, and on fusing with potash, gamboge, dragon's blood, kino, catechin, fustic, etc.

In order to obtain it from the gums they are fused with potassium hydroxide until the melt is quiet, the mixture dissolved in water, acidified with sulphuric acid, and shaken with ether, which removes the phloroglucinol and protocatechin or other acid resulting. After evaporating the ether, the residue is dissolved in water, the acid precipitated with a little lead acetate, the excess of lead removed by hydrogen sulphide and the phloroglucinol again extracted with ether.

When resorcinol is fused with sodium hydroxide phloroglucinol results.

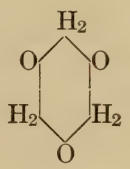
It crystallizes in colorless prisms with two molecules of water which may be entirely driven off at 100°. The anhydrous body melts 218–220° but a specimen will often begin to melt at 200° if heated slowly. It sublimes easily, is readily soluble in water, to which it imparts a sweet taste, and dissolves easily in alcohol and ether. Its aqueous solution is colored bluish violet by ferric chloride. It reduces Fehling's solution. Its solution in hydrochloric acid stains wood violet-red. Its alkaline solutions rapidly turns brown in contact with air owing to absorption of oxygen.

A cold solution of phloroglucinol in acetic acid reacts with potassium nitrite to form the trinitrosophloroglucinol, which separates on addition of potassium hydroxide and alcohol in the form of its potassium salt, a green, crystalline, explosive body.

Phloroglucinol, when dissolved in sulphuric acid and added to a mixture of nitric and sulphuric acids, yields the tri-nitro derivative melting 165 to 166° C. It is a yellow, explosive body which dyes wool and silk yellow.

When digested with acetyl chloride it yields the triacetyl derivative, melting 106°. By the phthalein fusion it gives a blue color on adding alkalies.

While in most of its reactions phloroglucinol behaves as symmetrical trihydroxy benzol, it also acts like a triketone, as it gives a trioxime, $C_6H_6(NOH)_3$, with hydroxylamine. It is possible that it exists in tautomeric forms, the second being represented by



a triketone of hexamethylene.

Phloroglucinol will be found occasionally in medicines intended for antiseptic, antipyretic, and tonic purposes.

Hydroxyhydroquinone

This phenol is prepared from pyrogallol by fusion with potash precisely as phloroglucinol is obtained from resorcinol. It melts 140°, is readily soluble in water, and its aqueous solution is colored greenish brown by ferric chloride, changing to blue and red on adding sodium carbonate.

THE NAPHTHOLS

Alpha- and beta-naphthol are monohydroxy derivatives of naphthalene and correspond with the monohydric phenols. Their properties are in many respects similar to those of the phenols; they dissolve in alkalies, forming metallic derivatives which are decomposed by acids and carbon dioxide, and yield acetyl and alkyl derivatives on the hydroxyl group. In other ways, however, the hydroxyl group is shown to be more sensitive than in the phenols, for heating with ammonia-zinc chloride to 250° the

corresponding amido compound is produced, the same reaction with phenol requiring a much higher temperature, and when heated with an alcohol and hydrogen chloride alkyl derivatives result.

Both α- and β-naphthol are of medicinal importance, but the latter and its derivatives have probably the most extensive use. They are antiseptic and germicidal in action and are used in ointments and washes in skin diseases, and internally are employed in the treatment of typhoid fever, chronic diarrhea, smallpox, scarlet fever, measles, etc. Alpha-naphthol is reported to be somewhat more powerful and weak solutions are credited with preventing the development of the spores of the tubercle bacilli.

Alpha-naphthol is a colorless crystalline substance with a faint phenol odor, melting 94°, boiling 278–280° C., readily soluble in alcohol and ether, but sparingly only in hot water. Its aqueous solution gives a scanty white or purplish-white precipitate with ferric chloride or a reddish color turning violet.

It is readily acted on by nitric acid, yielding a dinitro derivative, $C_{10}H_5(NO_2)_2 \cdot OH$, which crystallizes in yellow needles, melting at 130°, possessing marked acid properties, decomposing carbonates and forming deep yellow salts which dye silk a golden yellow. The sodium compound, $C_{10}H_5(NO_2)_2ONa + H_2O$, is known as Martius yellow.

When .5 gram of alpha-naphthol is dissolved in 10 mils of 1 per cent sodium hydroxide and boiled for one-half minute with 5 drops of chloroform a blue color appears, changing to bluish green and on standing four to five hours to a yellow green.

If .1 gram is mixed with .15 gram of picric acid and treated with 10 mils of boiling dilute alcohol (1 : 1) a picrate is formed, which when filtered, washed and dried on a porous plate melts on rapid heating at 188.5 to 189.5° C.

An aqueous solution of calcium hypochlorite gives a dark violet color changing to reddish brown.

Beta-naphthol forms colorless laminæ, melting 122° and boiling 285–6° C., soluble in alcohol, ether, chloroform, and fixed oils, but only slightly in cold water. Its aqueous solution gives an opalescence with ferric chloride or a pale-green tint. Its picrate, prepared as above, melts 155.5 to 156.8° C. When boiled with sodium hydroxide and chloroform a blue color is obtained which fades rapidly.

Calcium hypochlorite in aqueous solution gives a pale yellow color, destroyed on adding excess of the reagent.

Reuter has described a test for distinguishing between naphthalene and the two naphthols, using chloral hydrate as a reagent: One-tenth gram of the sample is mixed with 2.5 grams chloral hydrate and warmed for ten minutes; and simultaneous tests are run using in addition 5 drops

of strong hydrochloric acid in the one case and the same amount of acid and a piece of zinc in the other. The results are as follows:

		Naphthalene	α-Naphthol	β-Naphthol
Chloral Hydrate		Colorless	Ruby red, transparent, not fluorescent	Pure blue, transparent, not fluorescent
Chloral Hydrate	+HCl	Very slight pink	Intense dark greenish blue, not transparent	Intensely yellow, transparent
Chloral Hydrate	+HCl+Zn	Violet to brown	Dark violet blue. Water throws out a violet flocculent precipitate. Alcoholic solution violet with fluorescence	Dark brown. Water throws out a greasy precipitate. Alcoholic solution yellow with blue fluorescence

When a small quantity of the sample is treated with 2 mils of iodin in potassium iodide and an excess of sodium hydroxide added, alpha-naphthol gives a turbid liquid of an intensely violet coloration, and beta-naphthol a clear colorless liquid.

Estimation of Beta-Naphthol

Kuster [1] recommends digesting a weighed quantity of the sample in a sealed flask with reduced pressure, on a water-bath with a measured quantity of a saturated aqueous solution of picric acid. The naphthol is converted quantitatively into an insoluble picrate and the amount of picric acid remaining in solution is ascertained by titrating an aliquot portion with N/10 barium hydroxide. The picrate formed is slightly soluble in water, so that it is necessary to allow .0075 gram of beta-naphthol per 100 mils of the picric acid solution used.

Messinger and Vortmann's iodometric method for determining phenols has been adapted to beta-naphthol. Three grams of the sample are dissolved in a solution of not less than 3.5 grams sodium hydroxide and diluted to a known volume, not less than 250 mils. A 10-mil aliquot is placed in a small flask, heated to 55° C. and N/10 iodin added until the solution shows a yellow color. A greenish precipitate will settle on shaking. The cooled liquid is acidified with dilute sulphuric acid, made up to 250 mils and an aliquot titrated with sodium thiosulphate. The figure for the

[1] Ber., 1894, 27, 1101.

iodin actually used calculated to the whole amount taken and multiplied by .3784 will give the amount of beta-naphthol present.

Alphol

Alphol is the salicylic ester of alpha-naphthol, $C_6H_4(OH)COOC_{10}O_7$. It is a reddish-white crystalline powder, melting 83° C., insoluble in water, but soluble in alcohol, ether, and fixed oils. It is used as an antiseptic and antirheumatic.

Most of the naphthol derivatives which are encountered in practice are of beta-naphthol.

Alumnol

Aluminum Beta-naphthol-Disulphonate, $Al_2(C_{10}H_5 \cdot OH \cdot (SO_3)_2)_3$, the aluminum salt of beta-naphthol-disulphonic acid.

It forms a fine, nearly white, non-hygroscopic powder, soluble in 1.5 parts of water, forming a faintly acid and slightly fluorescent solution.

It is easily soluble in glycerin, but sparingly soluble in alcohol and insoluble in ether. When dried it loses about 9 per cent of water, and when exposed to the air it is darkened in consequence of its reducing properties. It is precipitated from solution by albuminous and gelatinous bodies, but these precipitates are redissolved in excess of the latter bodies.

The dried compound should yield 12.7 per cent of ash (alumina) on incineration. It is an astringent and mild antiseptic.

Beta-Naphthol Benzoate, $C_6H_5 \cdot COO \cdot C_{10}H_7$

It forms colorless needles, or a white crystalline powder, colorless and tasteless, melting at 110° C. It is almost insoluble in water, but readily soluble in alcohol and in ether; also soluble in chloroform, in glycerin and in olive oil.

It is decomposed by heating with caustic alkalies into naphthol and a benzoate which will then give their characteristic reactions.

To test beta-naphthol benzoate for the presence of beta-naphthol it should be shaken several times with dilute solution of sodium hydroxide (1 : 10) and immediately filtered. If beta-naphthol is present in considerable amount it will separate as a turbidity or precipitate after acidifying with dilute sulphuric acid. If the amount of beta-naphthol is small no precipitate appears, but the alkaline solution shows a bluish fluorescence and if it is boiled with chloroform a green color is produced.

It is used internally as an intestinal antiseptic in diarrhea and typhoid fever. Externally it is said to be useful as a parasiticide in the form of 3 to 10 per cent ointment.

Betol

Naphthalol—Naphthol-Salol—Salinaphthol. Betol is beta-naphthyl salicylate, $C_6H_4 \cdot OH \cdot CO \cdot O \cdot (C_{10}H_7)$, the salicylic acid ester of beta-naphthol.

It is a white, shining crystalline powder, colorless and tasteless, melting at 95° C. It is insoluble in cold or hot water or glycerin, difficultly soluble in cold alcohol or turpentine, easily soluble in boiling alcohol, in ether, in benzene, and in warm linseed oil. In the cold it is not changed by acids or alkalies of moderate concentration. When heated with alkalies it is decomposed into its constituents, which, if the solution is acidulated, will crystallize.

It is distinguished from salol by its higher melting-point and by the production of a brownish-green color, when a trace of nitric acid is added to its yellow-colored solution in pure sulphuric acid.

Bismuth Beta-Naphtholate

Bismuth beta-naphtholate occurs in the form of a brownish or grayish powder without odor, almost tasteless and insoluble in water. It is slightly soluble in alcohol.

From 1 to 2 grams of bismuth beta-naphtholate is shaken in a separator during one hour with 25 mils of chloroform and 25 mils of concentrated hydrochloric acid, and then 50 mils of water added and the mixture again shaken. The chloroform solution is then drawn off and the acid mixture extracted with three more portions of 10 mils each of chloroform and the combined extracts evaporated and dried to constant weight over sulphuric acid. A residue should remain, weighing at least 15 per cent of the material used, which should respond to tests of identity for beta-naphthol.

If bismuth beta-naphtholate is examined by the method given below, the bismuth oxide found should weigh not less than 60 per cent of the material taken.

The acid solution from which the naphthol has been extracted is transferred to a beaker, diluted to 200 mils, heated to boiling, ammonia water added till turbidity appears, then sufficient hydrochloric acid to clear up the turbidity, and then 50 mils of 10 per cent ammonium phosphate solution is added to the boiling liquid. The precipitate is allowed to subside, the clear liquid decanted through a tared porcelain Gooch crucible, the precipitate washed with hot water by decantation and finally transferred completely to the crucible. The precipitate and crucible are dried, placed in a nickel crucible, and exposed to the full heat of a Bunsen flame till the weight is constant. The weight of the resulting bismuth phosphate multiplied by .6869 should yield a figure (representing bismuth, Bi) equal to not less than 60 per cent of the material taken.

It is used in catarrhal and fermentative gastro-enteric disorders, such as gastritis, dysentery, and diarrhea.

Diiodobetanaphthol, $C_{10}H_6I_2O_2$

Iodonaphthol or naphtholaristol is a yellowish-green powder which decomposes on heating with evolution of violet fumes. It is insoluble in water, and only slightly in alcohol and ether, but dissolves readily in chloroform.

Betanaphthol Lactate

This substance, known as Lactol, is used as an antiseptic.

Sodium betanaphtholate is called Microcidin, and is employed as a constitutent of surgical dressings, and in antiseptic sprays for nose and throat diseases.

The naphthols combine with sulphuric acid to form a series of sulphonic acids.

The calcium salt of beta-naphthol sulphonic acid is called Abrastol or Asaprol, a reddish-white powder, soluble in water and alcohol, and decomposing at about 50° C. It has antiseptic, analgesic, and antipyretic properties and may be found occasionally in medicinal analysis.

Detection of Abrastol.—Sinibaldi's Method.—Make 50 mils of the sample alkaline with a few drops of ammonium hydroxide and extract with 10 mils of amyl alcohol (ethyl alcohol is added if an emulsion is formed). Decant the amyl alcohol, filter if turbid, and evaporate to dryness. Add to the residue 2 mils of a mixture of equal parts of strong nitric acid and water, heat on the water-bath until half of the water is evaporated, and transfer to a test-tube with the addition of 1 mil of water. Add about .2 mil of ferrous sulphate and an excess of ammonium hydroxide, drop by drop, with constant shaking. If the resulting precipitate is of a reddish color, dissolve in a few drops of sulphuric acid, and add ferrous sulphate and ammonium hydroxide as before. As soon as a dark-colored or greenish precipitate has been obtained introduce 5 mils of alcohol, dissolve the precipitate in sulphuric acid, and shake the fluid well and filter. In the absence of abrastol this method gives a colorless or light-yellow liquid, while a red color is produced in the presence of .01 gram of abrastol.

There are several phenols or phenol ethers occurring in essential oils which are in somewhat close realtionship, as they are all either allyl or propenyl derivatives of benzol. They usually have characteristic odors different in each case, and are the main ingredients identifying the particular oils in which they occur. It is impossible to describe these odors,

but when one becomes familiar with them they furnish the best evidence of their presence, and unless one is dealing with a straight oil, or has a sufficiently large sample, this odor is the best and often the only means of identification.

Chavicol, $C_6H_4(CH_2CH=CH_2)OH$, 1–4

Chavicol is a colorless liquid boiling about 237° with specific gravity 1.033 at 18°, occurring in bay and betel leaf oils. Its aqueous solution gives a deep-blue color with ferric chloride.

Methyl Chavicol, $C_6H_4(CH_2CH=CH_2)OCH_3$, 1–4

Methyl chavicol is a colorless liquid with a faint anise-like odor, boiling 215–216° C., sp. gr. .9714 to .972 at 15° C. It occurs in the oils of anise, star anise, fennel, bay, and basil oils. It is isomeric with anethol, which is the propenyl derivative, and may be converted to anethol by boiling with alcoholic potash. Estragol is also isomeric with methyl chavicol and occurs in tarragon oil.

Anethol, $C_6H_4(CH=CH\cdot CH_3)OCH_3$, 1–4

Anethol, or paramethyxypropenylbenzene, is also called anise camphor. It is a white crystalline substance with a strong anise-like odor, melting 21° C., boiling 233–234°, sp. gr. .985 to .986 at 21 to 25° C. It gives a well-defined bromin compound monobrom anethol dibromide, which melts 107 to 108° C. Anethol is the chief constituent of anise and star anise oils and is present in fennel.

Safrol, $C_6H_3(CH_2CH=CH_2)OOCH_2$, 1–3–4

Safrol is the methylene ester of allyl pyrocatechol and is a colorless or faintly yellow liquid with a characteristic odor of sassafras. It boils 233°, sp. gr. 1.108 at 15° C., and on cooling yields crystals which melt at 11° C. When oxidized with chromic acid piperonal (heliotropin) and piperonylic acid $C_6H_3OOCH_2\cdot COOH$ result.

Safrol is the characteristic and chief component of sassafras oil, and occurs in camphor oil. It has some use in medicine as a tonic, aromatic, and carminative.

By proper treatment it is transformed into the propenyl derivative isosafrol, $C_6H_3(CH=CH\cdot CH_3)OOCH_2$.

Eugenol, $C_6H_3(CH_2CH=CH_2)OCH_3OH$, 1, 3, 4

Eugenol is paraoxymetamethoxyallylbenzene, and is also called eugenic or caryophyllic acid. It is a faintly yellow liquid with the odor of cloves,

it boils 252° at 749 mm., sp. gr. 1.072 at 15°. Its alcoholic solution gives a bluish-green color with ferric chloride, but it gives only a transient grayish green in aqueous solution. Upon oxidation it yields vanillin and vanillic acid, and when treated with benzoyl chloride a benzoic ester is produced which melts 69–70° C.

Isoeugenol, boiling 260° C., the propenyl derivative, results on molecular rearrangement by boiling with alcoholic potash. Isoeugenol gives a blue-green with ferric chloride. Eugenol is soluble in alkalies and when shaken with ammonia is converted into a yellow crystalline mass.

A drop of concentrated sulphuric acid added to 10 drops of eugenol produces a blue color changing to purple on adding more acid.

Eugenol is an important constituent of clove oil and is also found in many others, including cinnamon, sassafras, pimento, bay, camphor, etc. It has antiseptic properties and is used as an ointment in skin diseases and tubercular affections and as an antiseptic in dentistry.

Methyl Eugenol, $C_6H_3(CH_2CH=CH_2)(OCH_3)(OCH_3)$, 1, 3, 4

Methyl eugenol has a less powerful though similar odor to eugenol, and boils 248–249°. It gives a bromin derivative melting 78° and on oxidation with permanganate is converted into veratric acid, melting 179–180°. It occurs in bay, citronella, hazelwort, paracoto bark, and other oils.

Eugenoform

Eugenoform is the sodium salt of a product obtained by the action of formaldehyde on eugenol. It forms colorless crystals soluble in water and alcohol and is used as an intestinal antiseptic in cholera and typhoid fever, and as a disinfectant.

Eugenol Benzoate

Benzoeugenol forms white crystals melting 68–70° C., soluble in alcohol, ether, and chloroform and is used in tuberculosis and for neuralgia.

Eugenol Cinnamate

The ester, melting 90°, forms odorless and tasteless shining needles soluble in ether, chloroform, and hot alcohol. It is used as an antiseptic in tuberculosis.

Asarol, $C_6H_2(CH=CHCH_3)(OCH_3)_3$

Ararol, asaronic, or asarum camphor, is propenyl trimethoxy benzene and occurs in the oils of hazelwort (Asarum europeum) and matico. It is an emetic and cathartic.

Asarol melts 62° and yields a dibromide melting 85–86° C.

Apiol, $C_6H(CH_2 \cdot CH = CH_2)(OCH_3)_2OOCH_2$

Apiol or parsley camphor is obtained from oil of parsley seed, Petroselium sativum, in which it occurs to the amount of about 25 per cent. It also occurs in the oil of the seeds and roots of celery, Apium graveolens. It crystallizes from ether, melting 36° and boils 294°. It is insoluble in water but dissolves in alcohol, ether, fixed, and volatile oils. Oxidizing agents convert it to apiol aldehyde, and on prolonged treatment to apiolic acid. By the action of nitric acid it is partially converted to oxalic acid and partly to a crystalline yellow nitro compound melting 116° C. Bromin in carbon bisulphide acts on apiol to produce tribromapiol, which may be crystallized out of alcohol, melting 88° C.

Commercial apiol has an oily consistency and is of varying composition. It is used as an emmenagogue and antiperiodic and is dispensed in capsules and in oily solutions, usually olive oil. Celery is used in dropsy and rheumatism and to a large extent in nerve tonics.

When apiol is boiled with alcoholic potash it is converted into isoapiol, the propenyl derivative, melting 56° and boiling 304°. It occurs in dill camphor.

Saligenin, $C_6H_4OH \cdot CH_2OH$

Saligenin is ortho-oxybenzyl alcohol and has the characters of both a phenol and an alcohol. It is one of the products of the hydrolysis of salicin, and can be prepared synthetically from carbolic acid and formaldehyde. It forms colorless to yellowish crystals, melting 86°, subliming 100°, soluble in alcohol, ether, and hot water. Its alcoholic solution gives a reddish-violet color with ferric chloride changing to yellow. With concentrated sulphuric acid a red color is produced. When boiled with anilin, oxybenzyl anilin is produced, melting 108°.

Saligenin is chiefly important as a means of identifying salicin, but it is also used to a slight extent as an antirheumatic.

Homosaligenin, $C_6H_3 \cdot CH_3CH_2OH \cdot OH$, 1, 2, 4

Homosaligenin melts 105°, gives a blue color with ferric chloride, and on boiling with dilute hydrochloric acid yields homo-saliretin, melting 200–205° C.

Diosphenol and Buchu

The leaves of Barosma betulina (Rutaceæ) are recognized as the official buchu. The therapeutic value of the drug is due probably to an essential oil, which contains as its chemically recognizable constituent, a phenolic and ketone-like body called diosphenol. The same or closely allied oil is present in the leaves of B. crenulata, which, however, is con-

sidered an adulterant of official buchu. It would be impossible, however, to detect the difference between these drugs in the extract form, the state in which they occur in medicinal preparations.

Buchu is valuable chiefly as a diuretic and is usually combined with some other kidney stimulant such as Juniper berries, potassium nitrate, triticum, and cornsilk. It will be found in many of the proprietary remedies recommended for kidney troubles, and is a constant component of kidney pills, and is often present in the trick pills containing methylene blue, which are used to deceive the unwary regarding the condition of their urine.

Liquid preparations contain buchu combined with juniper berries, cubeb, uva ursi, and nitrous ether; with juniper berries and potassium acetate; with Collinsonia, juniper berries, and Pareira; and small quantities of buchu are present in the "Buchu Gins" which used to be widely sold as medicinal beverages. Extract of buchu is present in cystitis pills combined with boric acid, triticum, cornsilk, Hydrangea, atropin, and potassium bicarbonate or benzoic acid, or Viburnum prunifolium. It is also combined with Hyoscyamus and potassium bicarbonate; and with Digitalis, squill, and potassium nitrate; and is present in certain capsule formulas combined with cubebs and copaiba.

In commerce round and long buchu leaves are distinguished; the first are those of B. betulina and B. crenulata; the second those of B. serratifolia.

E. M. Holmes reports the finding of three different species of leaves which closely resemble official buchu, and which might functionate as adulterants. The chief points of difference are as follows: Empleurum serrulatum, leaves acutely jointed, no gland at apex, odor different, and fruit consists of a single follicle with a sword-shaped beak: Barosma echloniana, leaves with rounded base, broader in proportion, thickened margin with very shallow crenulations, no gland at the very obtuse apex and a peculiar dull surface, the flowers have about six purplish glands on each petal: Psoralia obliqua, oblique or unequal sided lamina, recurved apiculus, veins hairy, and difference in structure of the oil glands.

The leaves of B. betulina yield on distillation from 1.3 to 2 per cent of oil, and from this the characteristic principle diosphenol separates on standing. The oil has a camphoraceous and mint-like odor. Diosphenol is called buchu camphor.

It is a colorless crystalline substance meiting 82°, boiling 232°, or at 112° under 14 mm., and has the properties of both a phenol and a ketone. It may be extracted from oil of buchu by alkalies, from which it is reprecipitated by acids, and forms an oxime and hydrazone. It gives a dark-green color with ferric chloride.

The presence of buchu is usually apparent by its characteristic odor.

This odor and the identification of the diosphenol in preparations containing appreciable quantities of buchu are the only means at present for identifying the drug. The odor should, of course, be compared with that evolved by a known sample. When the sample under examination is a pill or tablet, the characteristic constitutents of buchu can be separated by grinding, macerating with water, and subjecting to steam distillation. The distillate will contain the essential oil of buchu recognizable by its odor and on shaking with ether this will dissolve. From the ethereal solution the diosphenol can be shaken out with alkali, and recovered by acidulating and extracting with ether. Juniper oil will appear in the distillate if present originally in the sample and if in large amount may disguise the buchu, but the procedure for separating the diosphenol will eliminate the juniper constituents and enable one to detect the buchu, provided there is enough of it present.

Detection of Diosphenol

Make about 300 mils of the liquor distinctly acid and distill, taking off three fractions of about 100 mils each. Saturate the third fraction with salt and shake out with ether. Evaporate the ether *in vacuo*, take up residue in 4 to 5 drops of alcohol, add 1 to 2 drops alcoholic ferric chloride—a green color indicates buchu.

Confirmatory test can be made by testing a similar residue obtained as above with ammoniacal silver nitrate which should be reduced.

Juniper Communis

Extract of juniper berries and the oil of that fruit, are conveniently considered at this point in connection with buchu. The distilled oil and extract of Juniper communis (Pinaceæ) and probably of J. sibirica are chiefly used as adjuvants to more powerful diuretics in dropsical complaints, and to round out the formulas of pills and tablets designed to correct a deranged condition of the kidneys and genito-urinary tract.

The combinations of juniper and buchu will be found under the discussion of the latter drug, and as a general thing either juniper or buchu and often both together will be found in any proprietary remedy advertised as a remedy for diseases of the kidneys. Juniper is one of the components of elixirs of the " Swamp Root " type, where it is combined with emodin-bearing drugs, aromatic balsams, methyl salicylate, oil of cardamom, and cubeb.

Juniper oil has a characteristic odor and has been found to contain pinene and cadinene. Its specific gravity lies between .865 to .882, and it is usually lævogyrate up to $-11°$. It is miscible with all the organic solvents except diluted alcohol.

CHAPTER XX

SYNTHETIC ORGANIC NITROGEN COMPOUNDS

AMINES, DIAMINES AND AMIDES

THE nitrogen compounds in organic chemistry include numberless individuals. We have already considered a large class of them under the alkaloids, and the following discussion is concerned with those nitrogenous medicinal agents which are prepared synthetically.

ALIPHATIC NITROGENOUS COMPOUNDS

The simplest representatives of this group may be considered as substituted products of ammonia in which one or more of the hydrogens is replaced by an alkyl radicle. These bodies are called amines, and are primary, secondary, or tertiary, according as one, two, or three atoms of hydrogen has been displaced. The lower members are gases or low-boiling liquids and are strong bases, usually stronger than ammonia, fuming with nitric acid, combustible (thereby differing from ammonia), and forming double compounds with gold and platinum chlorides. The primary amines give the carbylamine reaction; and are converted by nitrous acid into primary alcohols with evolution of nitrogen. The secondary amines do not give the carbylamine reaction, and on treatment with nitrous acid yield a nitrosamine, which is detected by Liebermann's reaction. In order to perform this test the nitrosamine is separated and treated with concentrated sulphuric acid; a dark-green solution results which, after diluting with water, becomes red, and on adding excess of alkali assumes a blue or green color. The tertiary amines usually remain unchanged in presence of nitrous acid.

Moureu and Magnonac recommend the use of ethyl magnesium bromide for distinguishing the amines. When the reagent is dissolved in ether it reacts with primary and secondary amines in ether with the liberation of one molecule of C_2H_6 for each amine group present in the molecule. No reaction takes place with tertiary amines.

The amines occur among the decomposition products of animal and vegetable products, and in our work may be of moment only in rare instances; for example, in the examination of extracts of cod livers, or of oils prepared from animal matter which is in a state of partial decomposition.

Hydrazine, $H_2N\,NH_2$, is the parent substance of a large number of derivatives, some of which are of considerable importance.

Hydrazine sulphate, $NH_2 \cdot NH \cdot H_2SO_4$, called diamidogen or diamine sulphate, is a white crystalline solid, soluble in water and used as an antiseptic and fungicide.

Phenylhydrazine, $C_6H_5NH \cdot NH_2$

Phenylhydrazine is either a slightly yellow oil or a colorless crystalline mass, melting 23°. It boils with evolution of ammonia at 241–242°, and distills unchanged at 120° under 12 millimeters pressure. It is sparingly soluble in cold water, more readily in hot, and is very soluble in alcohol, ether, chloroform, and benzol. It is easily oxidized on exposure to air, becoming red and finally dark brown. It has strong basic properties and forms salts with acids and carbon dioxide. A solution of the hydrochloride reduces salts of silver, mercury, gold, platinum, and Fehling's solution in the cold, in the latter case nitrogen is evolved, and cuprous oxide precipitated, and anilin and benzol produced.

When the hydrochloride is treated with a cold solution of potassium nitrite, a yellow nitroso comp., $C_6H_5(NO)NNH_2$, separates, which on treatment with carbolic acid and strong sulphuric acid, yields a brown solution changing to green and blue.

Phenylhydrazine has well-marked antiseptic properties, and has been recommended as a substitute for mercuric chloride.

A solution of a salt of phenylhydrazine on treatment with caustic alkali yields a precipitate of the free base which is removable by shaking out with ether.

Phenylhydrazine reacts with aldehydes and ketones to form hydrazones, and when heated with excess of the reagent if the substance contains an OH group a second molecule reacts, producing osazones. It also forms hydrazides with hydroxy acids of the sugar group which have the general formula $RCOHNNHC_6H_5$,

Phenylhydrazine may be prepared from anilin by diazotizing and subsequently reducing the product thus obtained. It is interesting to note that under a strained interpretation of the term derivative, the well-known antipyrin could be considered a derivative of acetanilid because antipyrin can be prepared from phenylhydrazine, and anilin is one of the products of hydrolysis of acetanilid.

ANTITHERMIN

$$CH_3C(N \cdot NHC_6H_5)CH_2 \cdot CH_2 \cdot COOH$$

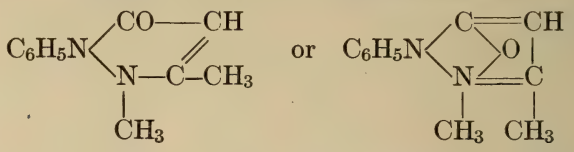
is the hydrazone of acetopropionic acid, which is $CH_3COCH_2CH_2COOH$. It forms colorless, odorless crystals from alcohol, melting 108°, nearly insoluble in water, but soluble in alcohol, ether, and dilute acid. It is

decomposed by alkalies with liberation of phenylhydrazine. It is used as an antiseptic and also in phthisis and Bright's disease.

Hydracetin is the acetyl derivative of phenylhydrazine, $C_6H_5HNNH(C_2H_3O)$, and is a colorless, crystalline powder, melting 128°, soluble in alcohol and hot water, and slightly in ether.

It is used as an antipyretic in rheumatic fevers, and externally in psoriasis and skin diseases.

Antipyrin—1 phenyl 2—3-dimethyl pyrazolone

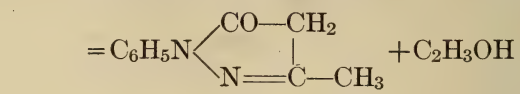


Antipyrin, known also as phenazone, analgesine, metozine, parodyne, phenylone, anodynine, antipyreticum, pyrazoline, sedatine, etc., has an extensive use in medicine as an antiseptic and analgesic, and to some extent as a hemostatic. It is used either by itself or in admixture for bilious and nervous headache, whooping-cough, puerpural fever, sea-sickness, gout, sciatica and neuralgic conditions. As a styptic it is used principally for hemorrhoids. It will often be found in tablets or elixirs mixed with caffein and the bromides, and occasionally acetanilid, acetphenetidin or codein will be included.

When phenylhydrazine reacts with ethyl aceto-acetate there ultimately is formed 1–3 phenylmethyl pyrazolone.

$$CH_3COCH_2COOC_2H_5+C_6H_5HNNH_2=CH_3C(NNHC_6H_5)CH_2COOC_2H_5+H_2O$$

$$CH_3C(NNHC_6H_5)CH_2COOC_2H_5+\text{heat}$$



On methylating the new substance with methyl iodide antipyrin results.

The first formula given above has been ascribed to Knorr and the second to Michaelis.

Antipyrin crystallizes in small, lustrous, rhombic needles or plates, odorless, and with a somewhat bitter taste, melting 113–114° unless it contains hygroscopic moisture, which reduces the melting-point to 105–107°, and which may be driven off at 100°. It sublimes when exposed to a temperature of 100°. It is very soluble in water, alcohol, and chloroform, very moderately soluble in ether, and but slightly in petroleum ether. It is removed from both acid and alkaline solutions by immiscible solvents, chloroform being the most efficacious and usually preferred in analytical work. Its aqueous solution is alkaline to methyl orange, but not to either litmus or phenolphthalein.

Antipyrin precipitates with a number of the alkaloidal reagents, including potassium mercuric iodide, iodin, picric acid, bromin water mercuric nitrate, potassium bismuth and potassium cadmium iodides, sodium phosphomolybdate, silicotungstic acid, and tannic acid.

Antipyrin dissolves in nitric acid with a yellowish color and on evaporating on the steam-bath a purple color develops. If the reaction is checked and water added, a violet precipitate is thrown down and the liquid is reddish purple in color. The purple coloration which results on evaporating with nitric acid will mask any test for atropin or strychnin which is subsequently made with alcohol potash.

When nitrous acid is added to a solution of antipyrin a green color is produced, and if the antipyrin is in quantity a precipitate of green crystals is obtained. The green substance which is visible at considerable dilution is due to isonitrosoantipyrin. On heating the liquid the color will change to purplish red. This test is best performed by dissolving a soluble nitrite in a little water, acidifying with sulphuric acid and then adding a solution of the suspected substance. It is not characteristic of antipyrin being given by other pyrazolones, but it is not given by acetanilid or the phenetidines. Pyramidon gives a blue to violet.

Antipyrin in dilute solution gives a blood-red color with 1 per cent ferric chloride solution. It is destroyed by excess of mineral acids.

It forms certain well-defined salts which are useful in substantiating its identification. The picrate, which is very insoluble in water, forms yellow crystals, melting 188°, the platinochloride, ferrocyanide and salicylate, the latter melting 91–92°.

Steensma [1] has described a reaction of antipyrin with *p*-dimethylaminobenzaldehyde which is useful for detecting small quantities of the substance, especially in toxicological work. The reagent consists of 1 gram of the above-mentioned substance, 5 mils of 25 per cent hydrochloric acid, and 95 mils absolute alcohol. A trace of the residue suspected of containing antipyrin is dissolved in a few mils of the reagent and evaporated in a porcelain dish, when a residue with red patches or a red ring is obtained. If the amount is extremely minute the reagent should be diluted with an equal volume of absolute alcohol. Pyramidon gives no color reaction, but salipyrin and acetopyrin react like antipyrin.

Primot [2] reports a reaction with vanillin which is carried out in the same way as the above test. The reagent is prepared by dissolving 1 gram vanillin in 6 mils dilute hydrochloric acid (1–1) and 94 mils of 95 per cent alcohol. If antipyrin is present the residue is characterized by a deep-orange ring and an orange deposit. Pyramidon does not show this color. Cryogenin (metabenzaminocarbazide) gives a yellow-green tint under the same conditions.

[1] Apoth. Zeit., 1097, 22, 819.

[2] Bull. Soc. Pharmacol., 1909, 370.

In the general scheme of analysis antipyrin will appear in considerable quantity in the residue left on evaporating the chloroform extraction from an acid solution. Traces of an alkaloid-like substance will have been evident in the previous fractions resulting from the petroleum ether, and ether extraction, but antipyrin is not removed to any extent by either of these solvents. If the residue left on evaporating the chloroform is syrupy in appearance and crystallizes in frostlike forms on cooling, and if it dissolves readily in water, gives a precipitate with potassium mercuric iodide, a green color with nitrous acid, a yellow picrate, melting 188°, and deep purple on evaporation with nitric acid, the analyst can feel satisfied that he has found antipyrin.

Pyramidon is the only substance in common use which might be mistaken for antipyrin. It melts, however, at 108°, gives a bluish-violet color with ferric chloride, a blue to violet with nitrous acid, and reduces silver nitrate after first yielding a blue color, antipyrin undergoing no change with silver nitrate.

From acetphenetidin or acetanilid it is easy to distinguish antipyrin, because neither is easily dissolved in cold water, and neither gives a precipitate with potassium mercuric iodide, and on hydrolysis with dilute acid acetphenetidin yields a solution which on dilution gives a blue color with bromide bromate reagent, and acetanilid yields anilin and acetic acid, and furthermore gives the carbylamin reaction.

COMPARATIVE REACTIONS OF ANTIPYRIN, PYRAMIDON AND TOLYLPYRIN

	Antipyrin	Pyramidon	Tolylpyrin
Melting-point	113–114 when anhydrous	108°	136–137°
Ferric chloride	Red-brown	Blue by reflected, violet by transmitted light	Violet
Silver nitrate	No change	Blue silver deposit	No change
Nitrous acid	Bright green	Blue to violet	Green
Nitric acid	Deep red	No red	Cherry red
Iodin solution	Brown red precipitate disappears on heating	Violet coloration; excess of reagent gives a turbidity which dissolves on warming	Red-brown precipitate which dissolves on heating
Bromin water	White precipitate	Concentrated solution gives a black or gray color	

In making quantitative estimations of antipyrin, the first step consists in separating it from the body of the product. This may be accom-

plished by treating the solution with a slight excess of sodium hydroxide and extracting three times with chloroform. If the specimen under examination is a pill or tablet in which antipyrin occurs by itself or with bromides, an aqueous solution may be rendered alkaline and shaken out with chloroform and on filtering, carefully evaporating the solvent in a tared dish and drying over sulphuric acid the antipyrin will be pure enough to weigh. If it is desired to check the figure by a volumetric estimation the following method may be employed:

To a concentrated aqueous solution of the antipyrin a slight excess of iodin solution (100 mils N/20 iodin containing 10 to 20 grams potassium iodide per liter and 4 mils hydroidic acid sp. gr. 1.7) is added and the flask well shaken until the precipitate adheres to the walls and the liquid becomes clear. The liquid is then filtered through a small asbestos filter and the residual iodin determined in an aliquot by titration with thiosulphate, 21.3 mils N/20 iodin = 0.1 gram antipyrin.

Lemaire [1] has suggested a volumetric method depending on the precipitation of the antipyrin by picric acid and titrating the excess of acid with sodium hydroxide. This procedure is of especial value when it is desired to estimate antipyrin alone or in the presence of caffein, as the latter has no influence.

ASSAY OF LIQUID HEADACHE MIXTURES

Method Involving the Precipitation of Antipyrin with Mercuric Nitrate and Purification of Caffein.—Measure 25 mils of the sample accurately with a standardized pipette or measuring flask, washing out the graduate and introducing into a 16 oz. separatory funnel (Squibb type). Add a slight excess of 10 per cent sodium hydroxide, shake out with four 50-mil portions of chloroform. Each shake-out should consume at least five minutes and the separator be allowed to stand for about five minutes after each shake-out in order that the solvent may completely separate. Run off the chloroform from each extraction into another separator, and when the four shake-outs have been united, run into a flask of about 300 mils capacity and recover the bulk of the chloroform, which can be used over again for subsequent extractions. Finally, run the residual chloroform into a tared beaker or dish, wash out the flask with a little pure chloroform, evaporate over a steam- or water-bath, using a fan or air pressure to hasten the volatilization of the solvent; dry the residue for about an hour at a temperature of 100° and weigh. Dissolve the residue in the beaker in about 25 mils of water. Pour the mixture into a 100-mil graduated flask, wash out the beaker with a little water and add an excess of mercuric nitrate solution (1 : 3). This is best accom-

[1] Pharm. J., 1905, 74, 13.

plished by adding the reagent in small quantities at a time, allowing the precipitate to settle and observing when no further addition of the reagent produces a precipitate. Then make up to the mark with distilled water and shake thoroughly. When the precipitate has settled, filter off one-half of the liquid in a flask, amounting to 50 mils and shake out four times with 50-mil portions of chloroform. Unite the chloroform extractions, add 10 mils of dilute ammonia water, and shake throughly. Run the chloroform into another separator and shake out with water; then run the chloroform into a flask, recovering the greater portion as above, and then evaporate the remainder in the same flask, over a steam-bath, using a current of air to hasten the evaporation. When all the chloroform has been driven off, add 15 mils of dilute hydrochloric acid and 15 mils of iodin solution (10 mils of iodin—20 mils of potassium iodide—100 mils water). Allow this to stand overnight, tightly corked. Filter onto a dry filter and wash twice with about 10 mils of iodin solution. Then transfer the filter containing the precipitate back into the flask in which the precipitation was made; add 15 mils of water and about one-third of a gram of sodium sulphite and a drop of dilute sulphuric acid. Warm, and as soon as the precipitate has dissolved and there is no further color of the iodin left, filter into a separator, neutralize with ammonia, and shake out five times with chloroform, using the following amounts: 25—15—15—10—10 mils.

Unite the chloroform extractions, insert a pledget of cotton into the stem of the separator which has been previously dried with a piece of filter paper, run the chloroform through the stem into a tared dish, washing out the inside of the separator once with about 5 mils more chloroform, evaporate the solvent, and weigh the residue as caffein. This weight multiplied by 2 and subtracted from the total weight of the mixture of antipyrin and caffein will give the weight of the antipyrin. By multiplying this figure by 1.18, the amount of antipyrin in one fluid ounce of the mixture will be obtained, and referring to a comparative table the amount in grains may be read off.

Method Involving the Precipitation of Antipyrin with Picric Acid and Titrating the Excess of the Reagent.—Measure out a 25-mil sample of the product as described in the previous method, transfer to a separator, add an excess of sodium hydroxide, shake out four times with 50-mil portions of chloroform, unite all the chloroform extractions obtained, wash with about 10 mils of water, and then run the chloroform through a pledget of cotton into a flask for recovery. Recover the bulk of the solvent and finally evaporate the balance over a steam-bath and leave the residue in the flask in which the distillation was made. After the solvent has been entirely driven off, add about 10 mils of water and warm. Transfer the aqueous liquid to a 50-mil graduated flask, washing out the

distilling flask with a little water to make sure that all of the antipyrin and caffein is removed, and finally make up to the mark with distilled water. Shake thoroughly, remove 10 mils with a pipette, and transfer to a small flask. Add from a burette exactly 40 mils of N/20 picric acid; shaking as the addition is made. Allow the solution to stand for about an hour, then filter off through a dry filter exactly 25 mils, using a graduated flask to obtain the proper quantity. Transfer the aliquot to a flask of about 100 mils capacity, washing out the graduate and adding about 25 mils of water. Add two or three drops of phenolphthalein and titrate with an exactly N/10 solution of sodium hydroxide. The end-point is reached when one drop of the acid produces a color which does not fade and which resembles in shade the color of the solution of acid bichromate of potassium.

A blank must be run on 40 mils of the picric acid solution used. The calculation is as follows:

Multiply the number of mils of N/10 alkali required to titrate the excess of picric acid by 4 and subtract this figure from the number of mils of N/10 alkali required to neutralize the 40 mils of picric acid. Multiply this figure by .009338 and the product by 5. which will give the amount of antipyrin in the 25-mil sample taken.

It is not necessary to have an exact known solution of picric acid, but it should be made approximately N/20, as a solution of stronger concentration cannot be obtained, and if a blank is run, its equivalent in terms of N/20 picric acid is easily obtained.

Emery recommends the following methods for determining antipyrin and the ingredients accompanying it in various combinations.

Method of Analysis of Headache Mixtures Containing Antipyrin, Acetphenetidin, and Codein Sulphate.—Antipyrin may be estimated gravimetrically as in the case of caffein, or volumetrically by means of a standard alcoholic solution of iodin in the presence of mercuric chloride. Its separation from acetphenetidin or acetanilid is easily effected by means of chloroform, after subjecting a mixture to hot digestion with dilute sulphuric acid, whereby the arlyamids are changed into the corresponding sulphates.

Ascertain the weight of 20 tablets, then weigh out an amount of the finely powdered sample equal to the average weight of one tablet, transfer to a separatory funnel, add 50 mils of chloroform, 10 mils of water, and a few drops of dilute sulphuric acid. Shake vigorously, allow to clear, then draw off through a pledget of cotton and a small dry filter into a 200-mil Erlenmeyer. Repeat the extraction four times, distilling off a portion of the solvent on completion of the third shake-out, in order to accommodate the chloroform from the final two extractions in the same flask. On completion of the fifth and final shake-out, distill the chloroform down

to about 10 mils add 10 mils of dilute sulphuric acid (1 : 10 by volume), continue heating gently until all the solvent has passed over, remove to steam-bath, and digest till the volume of liquid amounts to about 5 mils, add 10 mils of water, and continue the treatment until the liquid is again reduced to 5 mils. In order that the hydrolysis may be complete, that is, no particles of acetphenetidin remain on the sides of the flask, rotate the latter gently from time to time during the process of digestion, or better, perhaps, add a few drops of alcohol or chloroform now and then.

Antipyrin.—Transfer the aqueous acid solution of phenetidin sulphate and unchanged antipyrin to a separatory funnel by the aid of water, so that the final volume does not exceed 20 mils. Make seven extractions with 30-mil portions of chloroform, clearing and drying the solvent by means of a cotton pledget and dry filter as hereinbefore described. Distill the united chloroformic extractions down to about 10 mils, transfer to a tared 50-mil beaker, evaporate on a steam-bath to apparent dryness; cool, and weigh. It has been found that antipyrin retains traces of moisture and chloroform with great obstinacy, hence several days are required, even with the help of a vacuum desiccator, to approximate to a constant weight. It is therefore more expeditious to subject the crude residue to volumetric estimation. To this end dissolve the antipyrin in 95 per cent alcohol, transfer to a 100-mil graduated flask, and fill to the mark. Titrate an aliquot (20 mils or more if the amount of antipyrin is relatively small) of the alcoholic solution of antipyrin thus prepared with an iodin solution prepared and standardized in the following manner: Make up three solutions—*A*, containing 1.351 grams of resublimed iodin in 100 mils of 95 per cent alcohol; *B*, containing 1 gram pure antipyrin in 100 mils of 95 per cent alcohol; *C*, containing 5 grams of mercuric chloride in 100 mils of 95 per cent alcohol. Into a 100-mil Erlenmeyer measure from a burette 20 mils of Solution *B*, and by means of a pipette 10 mils of Solution *C*, then run in from a burette the iodin solution until a faint yellow coloration persists after a lapse of three to five minutes. Run several duplicates and it will be found that, under the conditions obtaining in the experiment, approximately 20 mils of the iodin solution thus standardized will very nearly correspond to 1 mil of antipyrin solution, or, by weight, 10 mg. of antipyrin. The value of the iodin solution in terms of antipyrin having been thus determined, subject the aliquot of the alcoholic solution of antipyrin from sample under examination to a similar treatment, basing the final result on an average of two or more titrations.

Since the presence of either acetphenetidin or codein is apparently no bar to the accuracy of the above reaction, it is wise to check the value for antipyrin already obtained by treating the original sample as follows: Weigh out on a small (5.5 cm.) filter an amount of the powdered sample

equal to the average weight of one tablet, wash with successive small portions of 95 per cent alcohol, in quantity about 20 to 30 mils, sufficient at least to remove all the antipyrin in the mixture. Collect solvent in a 100-mil Erlenmeyer, add 10 mils of solution *C*, then run in the standard iodin until a faint yellow coloration persists. The number of cubic centimeters of iodin required to effect this should agree approximately with the value previously obtained.

Acetphenetidin.—Wash the filter used to dry the chloroform solution of antipyrin once with 5 mils of water, allowing the latter to run into the separator containing the phenetidin sulphate. Treat the solution with successive small portions of solid sodium bicarbonate until an excess of this reagent, after complete neutralization of the sulphuric acid, persists at bottom of the liquid. Now add 60 mils of chloroform and, for every 100 mg. of acetphenetidin known or believed to be present, about 5 drops acetic anhydride; shake for some time vigorously, allow solvent to clear, then pass through cotton, and dry filter into a 200-mil Erlenmeyer, exactly as in the extraction of caffein. Distill over 50 mils of the chloroform, make up to 60 mils with fresh solvent, and extract again. Draw off chloroform, distill as before, this time about 60 mils, then make a third and final extraction. Distill to about 10 mils, transfer by pouring and rinsing with small quantities of chloroform to a tared 50-mil crystallizing dish, evaporate on the steam-bath to apparent dryness, finally removing any considerable excess of acetic anhydride by repeated additions of about 1 mil of fresh chloroform, containing 1 to 2 drops alcohol. The acetphenetidin should finally appear as a whitish, crystalline mass, having usually a faint acetous odor. This will entirely disappear on standing some time in the open, or more quickly in a vacuum desiccator over lime. The residue should be repeatedly weighed until it suffers no further loss.

Codein Sulphate.—The estimation of codein can be carried out during the hydrolysis of acetphenetidin. Wash the filter used to dry the chloroform solution of antipyrin and acetphenetidin once with 5 mils of water, receiving latter in the separator containing the aqueous-acid solution of codein. Add solid sodium bicarbonate in slight excess, then extract three times with 50 mils of chloroform. Clear, dry, and collect solvent from the three operations in a 200-mil Erlenmeyer, then distill down to 10 mils. Transfer to a 50-mil tared beaker, evaporate to apparent dryness on the steam-bath, moisten the amorphous residue with a few drops of alcohol, evaporate again, cool, and weigh. This weight, multiplied by the factor 1.3144, will give the amount of codein sulphate originally present in the sample. It is recommended that this result, which is likely to be somewhat high, be verified by titrating the crude codein with N/50 sulphuric acid, using 1 drop of methyl red solution as indicator.

In the event that acetanilid instead of acetphenetidin is employed in combination with antipyrin and codein sulphate, it would be necessary to modify the procedure only as regards the final treatment of the aqueous acid solution containing in addition to antipyrin the acetanilid, which after being subject to hydrolysis and freed from the former is titrated with potassium bromide-bromate.

ESTIMATION AND SEPARATION OF ANTIPYRIN FROM VARIOUS SYNTHETIC PRODUCTS BY MEANS OF ITS PERIODIDE.[1]

Direct estimation when no other substance is present which will itself or after treatment with iodin be extracted by chloroform.

Method I.—Aqueous solution of the antipyrin (containing not over .25 gram antipyrin in 10 mils water) is poured into a large separatory funnel, 20 mils saturated sodiun bicarbonate solution is added, a few mils of washed chloroform (to remove alcohol), 100 mils water and about 50 mils of approximate N/10 iodin is added. The solution is shaken thoroughly about six times at intervals. The excess of iodin is removed by adding a few mils of sodium thiosulphate and shaking. The resulting iodoantipyrin is shaken out with three 30-mil portions of chloroform and washing each extract with about 10 mils water in a small separatory funnel and filtering through cotton into a tared 150-mil Erlenmeyer to a condenser, and chloroform distilled down to recover most of the the chloroform, until about 10 mils remain. This is then evaporated to dryness on the water-bath (preferably over a blast) and dried in oven at 110° C. for half hour.

Multiply the iodoantipyrin by factor .5992 (H = 1) to antipyrin.

DETERMINATION OF ANTIPYRIN. SEPARATION BY PERIODIDE METHOD FROM ACETANILID, SULPHONAL, AND PHENACETIN

Method II.—To an aqueous solution of antipyrin (not *over* .25 *gram* in about 50 mils water) in a 500-mil Erlenmeyer flask, add 20 mils strong hydrochloric acid, about 100 mils of approximate N/10 Iodin in potassium iodide, shake well and allow tarry precipitate to settle clear (should be allowed to stand at least three hours). Ten mils hydrochloric acid is sufficient if allowed to stand overnight. Pour off the clear supernatant liquid through a funnel plugged and overlaid with glass wool and a little asbestos. Wash the tar by decantation about eight or nine times with about 20 mils acid water (5 per cent HCl solution) each time keeping as much of the tar in the flask as possible. Then place the funnel containing some of the tarry precipitate in a large separatory funnel, dissolve

[1] W. O. Emery and S. Palkin. J. Ind. & Eng. Chem., 1914, 6, 751.

the tar in the Erlenmeyer by warming slightly with about 50 mils of *methyl* alcohol (free from ethyl alcohol and acetone) making sure that *all* the tar is in solution, pour through funnel into the separatory funnel, thus dissolving the tar left on the glass wool. Wash Erlenmeyer and funnel several times with *methyl* alcohol from a wash bottle until everything (all the tar) has been washed in the separatory funnel. Add 30 mils saturated sodium bicarbonate solution, dilute with about 50 mils water, shake thoroughly three to four times at intervals, allowing to stand a few minutes each time. Remove the excess of iodin with a few mils of strong sodium thiosulphate solution, now shake out the resulting iodoantipyrin with 40 mils chloroform, draw off the chloroform extract into a small separatory funnel and wash with about 10 mils water, and filter through cotton into a tared 150-mil Erlenmeyer. Repeat this operation twice with 40 mils chloroform each time, using the same wash water, (three times in all). Distill the chloroform extracts to recover most of chloroform as described in method I, and finally evaporated to dryness on steam-bath, dry in oven at 110° for half-hour and weigh the iodoantipyrin.

Multiply the iodoantipyrin by the factor .5992 (H=1) to obtain tne amount of antipyrin.

ASSAY OF TABLETS CONTAINING CAFFEIN AND ANTIPYRIN IN ADMIXTURE

Method.—Weigh out on a metal scoop or watch-glass 0.25 gram of the sample, transfer to a 150-mil separatory funnel with 5 mils alcohol-free chloroform and 10 mils water, add 0.5 gram sodium bicarbonate and about 10 mils N/5 iodin (or double the quantity of N/10 iodin), then shake vigorously one minute, after which operation a slight excess of iodin should still be apparent in the liquid menstruum, provided all the antipyrin has been converted to iodoantipyrin. If, however, all the iodin has been thus expended, a little more should be added and the mixture again shaken. Now discharge the uncombined iodin by means of a small crystal of sodium thio sulphate, add 20 mils U. S. P. chloroform and shake. After clearing, draw off solvent into a second separator containing 5 mils water, shake, and after clearing pass the chloroform through a small dry filter into a tared 50-mil beaker, evaporate to apparent dryness on the steam-bath, accelerating this operation by means of an air blast, if available. Repeat extraction with two (three, in case N/10 iodin were used) 25-mil portions of chloroform, washing, filtering, and evaporating each portion in rotation substantially as directed for the first portion. Recover all traces of crystalline products separating about tips of funnels and edge of filter by judicious washing with chloroform.

The final colorless, crystalline residue of caffein and iodoantipyrin is dried one-half hour at 100°, then cool, and weigh. Designate this weight *A*.

Dissolve this residue in 5 mils glacial acetic acid, add 10 mils saturated aqueous solution sulphur dioxide, then transfer the resultant liquid by pouring and rinsing with hot water to a 400–500 mil beaker, until the final volume amounts to about 200 mils. Add aqueous silver nitrate solution (containing about 0.25 gram silver nitrate) and follow with a few drops of nitric acid, then heat nearly to boiling, stirring the while in order to agglomerate the silver iodide. Add about 15 mils conc. nitric acid, cover beaker with watch-glass and boil gently five minutes. Filter by decantation through a tared Gooch, wash precipitate twice with boiling water, finally transferring the silver iodide completely to the Gooch, washing several times with hot water and finally with alcohol. Dry one-half hour in air bath at 110°, cool, and weigh.

The weight of silver iodide multiplied by the factor 0.8012 yields the quantity of antipyrin present in sample taken. The quantity of caffein present in sample is ascertained by subtracting the product, obtained by multiplying the weight of silver iodide by the factor 1.3374, from the weight designated *A*.

ASSAY OF LIQUID HEADACHE MIXTURE CONTAINING ANTIPYRIN AND CAFFEIN

Method.—By means of a pipette standardized at 20°, transfer 10 mils of the solution, previously warmed or adjusted to 25°, to a 150-mil separatory funnel containing 0.5 gram sodium bicarbonate. Add about 15 mils N/5 iodin (or double the quantity of N/10 iodin), then shake vigorously one minute. All succeeding operations are identical with those outlined for the powder mixture.

Comments and Suggestions.—The foregoing procedure is based on the fact that, when an aqueous solution of iodin and sodium bicarbonate is permitted to react with antipyrin, whether alone or with other substances as caffein, mono-iodoantipyrin is formed. This latter substance, together with caffein, is thereupon extracted with chloroform, the weight of such mixture ascertained and the iodin therein estimated as silver iodide, from which the antipyrin is calculated by means of the appropriate factor. In view of the somewhat radical treatment with dilute nitric acid, to which the caffein is necessarily subjected incidental to the precipitation of silver iodide, a direct determination of that substance is impracticable. The quantity of caffein is, however, ascertained by subtracting the amount of iodoantipyrin, as calculated from the silver iodide, from the combined weight of caffein and iodoantipyrin.

The use of alcohol-free chloroform is specified in order to preclude the possible formation of iodoform, the presence of which would necessarily render the method valueless.

The final washing of the silver iodide with alcohol should be thorough in order to eliminate certain unidentified organic substances arising from the action of nitric acid on the antipyrin complex.

There are several antipyrin compounds used medicinally.

Antipyrin Salicylate, $C_{11}H_{12}N_2O \cdot C_6H_4OH \cdot COOH$

is a weak chemical combination of antipyrin and salicylic acid.

It occurs as a white, coarsely crystalline powder, or in hexagonal tabular crystals, melting at 71 to 92° C., odorless, slightly sweet, soluble in alcohol, less readily in ether. It is decomposed by acids with the elimination of salicylic acid, and by alkalies with the elimination of antipyrin.

Its aqueous solution is rendered milky by tannic acid, then colored green by the addition of a few drops of fuming nitric acid. It is colored deep red by ferric chloride, passing to violet red on copious dilution with water.

Tussol—Antipyrin Mandelate, $C_{11}H_{12}N_2O \cdot C_6H_5 \cdot CHOH \cdot COOH$,

a salt of mandelic acid, $C_6H_5CHOH \cdot COOH$, and antipyrin. It is a white crystalline powder, having a bitter taste and melting at 52 to 53° C. It is soluble in 15 parts of water, 3 to 4 parts of alcohol, or 25 to 26 parts of ether, producing solutions of acid reaction. When heated above the melting-point, it gives off the odor of bitter almonds, and finally burns without leaving a residue. It is split into its constituents by milk and by alkalies.

Its aqueous solutions give the reactions for antipyrin; if warmed with potassium permanganate it develops the odor of benzaldehyde, but is not effected by silver nitrate, barium nitrate, dilute sulphuric acid, or hydrogen sulphide; useful in the treatment of whooping-cough.

FERROPYRIN, $(C_{11}H_{12}N_2O)_3 \cdot (FeCl_3)_2$

Ferropyrin is a compound of antipyrin and ferric chloride, containing about 35 per cent of ferric chloride and 64 per cent of antipyrin.

It is a yellowish red, crystalline powder, having an acid-astringent taste. It is soluble in 5 parts of cold water, but requires 9 parts of hot water for solution; it is soluble in alcohol, but insoluble in ether.

It should form a clear blood-red solution in water. Its aqueous solution 1 : 5 yields a precipitate of ferric hydroxide on addition of ammonia

in excess, and the filtrate should give no reaction for nitric or sulphuric acid, nor heavy metals, and should yield a residue on evaporation, which is completely volatilized when heated on platinum. After acidification with nitric acid, the filtrate yields a white precipitate with silver nitrate and in the filtrate from this the antipyrin may be detected by means of ferric chloride or by nitrous acid.

It is hematinic, hemostatic, astringent, analgesic, and tonic.

Antipyrin Iodide—Iodopyrin

The compounds of iodin and antipyrin have been studied by Emery as noted under the methods for the quantitative determination of the base. One of these which is claimed to contain but one atom of iodin is used to a limited extent as an antipyretic, alterative, and analgesic in tuberculosis, syphilis, typhoid fever, bronchitis, and asthma.

Antipyrin Monobromide

A compound analogous to the one previously mentioned, but containing bromin instead of iodin, is called bromopyrin, and is used as an antipyretic and antiseptic. It melts 114° C. The name "Bromopyrin" is applied to mixtures of the general type of caffein, antipyrin, and alkali bromides.

Methylenediantipyrin—Fermopyrin

This product results from heating together antipyrin and formaldehyde.

Methylenediantipyrin tetrabromid, salubrol, has been described under formaldehyde. Salubrol is an orange-yellow powder, melting 155° and used as a substitute for iodoform.

Antipyrin Salicylacetate

There seem to be two products bearing this name, one of which is a salt of acetylsalicylic acid and the other a somewhat uncertain mixture. They combine the virtues of antipyrin and salicylic acid, and are hence used in rheumatic condition where an analgesic is required.

The salt of acetylsalicylic acid is also called acetopyrin and acopyrin, and the other product pyrosal.

Antipyrin Resorcylate—Resalgin

Resalgin or resorcylalgin purports to be a salt of betaresorcylic acid and forms colorless needles melting 115° C. It is used as an antiseptic.

Resopyrin

Resopyrin differs from resalgin in that it is a product resulting from the fusion of molecular proportions of resorcin and the base. It is another of those compounds where chemical individuality is a matter of doubt.

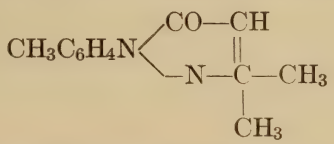
Chloral hydrate and antipyrin combined are called Hypnal, and the crystalline product melts at 67° and is used in cases of insomnia and spasmodic cough. It reduces Fehling's solution, gives a blood-red color with ferric chloride and chloroform on boiling with alcoholic potash.

Antipyrin and paramidobenzenesulphonate produce sulphopyrin, and a mixture of carbolic acid and the base is called Phenopyrin.

It will be noted from a survey of the above products that while there are a few well-defined salts of antipyrin, the majority of the compounds are of a more or less doubtful nature. Antipyrin is not a strong base chemically and hence a hard and fast union with the weak acids and phenols is not to be expected. While it is not questioned that an equilibrium of greater or less stability may be obtained as the result of a fusion, the ease with which the compounds are separated and identified when subjected to the simple action of water is sufficient to show that no very permanent compound has been formed.

Paratolyldimethylpyrazole

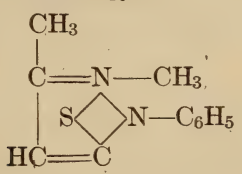
Tolylantipyrin is prepared by treating paratolylhydrazine with acetoacetic ester and methylating the resulting product.



It is a colorless crystalline substance with a bitter taste and melts 136–137°. It resembles antipyrin in its physiological properties, and might at first be mistaken for it, but the difference in its chemical characteristic will be noted in the table of comparative reactions on page 794.

The salicylate of this base is called Tolysal. It is analogous to antipyrin salicylate, and is used as an antineuralgic and antirheumatic.

Thioantipyrin

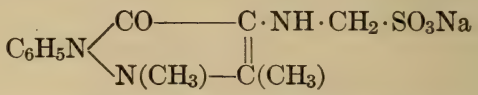


Melts 166°. It gives a transient green color with ferric chloride, but not with nitrous acid.

Selenopyrin melts 168°. It gives no color with ferric chloride and only a faint green with nitrous acid.

Melubrin

Melubrin is sodium 1-phenyl-2, 3-dimethyl-5-pyrazolon-4-amido-methan-sulphonate,



the sodium salt of 1-phenyl-2, 3-dimethyl-5-pyrazolon-4-amido-methan-sulphonic acid, differing from antipyrin in that a sodium-amido-methan-sulphonate group, $\cdot NH \cdot CH_2SO_3Na$, has replaced a hydrogen atom of the pyrazolon group.

It is a white, odorless, almost tasteless crystalline powder, readily soluble in water, but slightly soluble in alcohol. The aqueous solution is neutral in reaction but unstable.

If about 0.2 gram of melubrin dissolved in 5 mils of water is boiled with 3 mils of diluted hydrochloric acid, sulphur dioxide and formaldehyde will be liberated.

If one-half of the solution thus formed is treated with 3 drops of sodium nitrite solution and 5 mils of an alkaline solution of betanaphthol, a red precipitate will be produced.

If the remainder of the above solution is treated with 1 gram of sodium acetate and 15 mils of a saturated aqueous benzaldehyde solution, a yellowish-white, flocculent precipitate will be formed which, when washed and dried, will melt at 173°.

If 0.4 to 0.5 gram of melubrin is weighed into a platinum dish, treated with dilute sulphuric acid, and heated to constant weight, the sodium sulphate thus formed should weigh 0.2160 to 0.2250 gram for each gram of material used, representing a sodium content of 6.99 to 7.28 per cent. It is used as a antipyretic in fever and is analgesic.

Iodomethyl Phenylpyrazolon

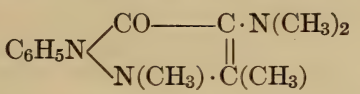
A substance claiming to be an iodin derivative of this character is sold under the name of Mydrol. It is soluble in water and alcohol and is used as a mydriatic.

Pyramidon

The use of pyramidon in medicine is probably on the increase, and the analyst may encounter it in any new mixture intended for antipyretic purposes. Especial note is made of this because a worker experienced

in the analysis of medicines knows that there are practically only three antipyretics in general use and that the extent of their prevalence is in the following order, acetanilid, acetphenetidin, and antipyrin.

Pyramidon is phenyl-dimethyl-dimethylamino-pyrazolon,



differing from antipyrin in that a dimethylamino group, $N(CH_3)_2$, has replaced a hydrogen atom of the pyrazolon nucleus.

It is prepared by the reduction of nitroso-antipyrin to amidoantipyrin and treating this with methyl chloride or iodide.

It forms small, colorless, slightly alkaline crystals, melting at 108° C.; almost tasteless; soluble in 11 parts of cold water and readily soluble in alcohol, ether, and benzene. Its aqueous solution saturated at 70° C. deposits oily globules of pyramidon on boiling.

Ferric chloride colors the neutral or slightly acidulated solution of pyramidon a bluish-violet color; nitrous or nitric acid produces a fugitive blue-violet color; silver nitrate produces an intense violet coloration when added to the aqueous solution, followed by the formation of a black precipitate of metallic silver, and the same color is produced by platinum chloride, by ammonium persulphate, and by lead dioxide. In hydrochloric acid solution pyramidon gives a fine crystalline double salt with mercuric chloride.

Pyramidon may be estimated by means of picric acid by the same process as antipyrin.

Pyramidon Acid Camphorate, $C_{13}H_{17}N_3O \cdot C_{10}H_{16}O_4$

is an acid salt of pyramidon and camphoric acid. It is a white, crystalline powder of acid reaction, melting (indefinitely) at 84 to 94° C., soluble in 20 parts of water or 4 parts of alcohol.

It gives the characteristic reaction of pyramidon with silver nitrate. If the solution in hot water is made alkaline with caustic soda, the pyramidon may be shaken out with chloroform; if the residual aqueous liquid is then acidified with sulphuric acid the camphoric acid (melting-point 186° C.) may be shaken out with ether.

Pyramidon Neutral Camphorate, $(C_{13}H_{17}N_3O)_2 \cdot C_{10}H_{16}O_4$

is a neutral salt of pyramidon and camphoric acid. It is a white, crystalline powder, melting (indefinitely) at 80 to 90° C. It dissolves with acid reaction in 15 parts of water or 2 parts of alcohol.

Pyramidon Salicylate, $C_{13}H_{17}N_3O \cdot C_7H_6O_3$

is a salt of pyramidon and salicylic acid. It is a white, crystalline powder, having an acid reaction and melting indefinitely at 68 to 70° C. It is soluble in 16 parts of water or 5 to 6 parts of alcohol.

The aqueous solution is colored intensely red by ferric chloride, and produces a white precipitate with silver nitrate, the solution assuming a violet color after a short time.

Trigemin

Trigemin is prepared by combining butylchloralhydrate and pyramidon, and is used as an analgesic and sedative. It is soluble in water and other ordinary organic solvents except petroleum ether, which has but slight action, and melts 83–85°.

Arhovin, $C_{10}H_{13} \cdot C_6H_4(COOC_2H_5)(C_6H_5)_2NH$

Arhovin is an addition product of diphenylamine and thymylbenzoic acid. It is an oily liquid, with an aromatic odor and a cooling and afterward burning taste. It is insoluble in water, but dissolves in alcohol, ether, chloroform, and oily liquids and is employed as an antiseptic in venereal troubles.

Agathin—Salicylalphamethyl Phenylhydrazone, $C_6H_5 \cdot N(CH_3)N : CH\ C_6H_4OH$

Agathin is a reaction product of alphamethyl phenylhydrazine and salicylic aldehyde. It forms yellowish crystals melting 74° C., soluble in alcohol, ether, and benzol, but insoluble in water. It is used as an antirheumatic and antineuralgic.

DIAMINES

The diamines are derived from a double molecule of ammonia by the replacement of two or more of the hydrogen atoms by hydrocarbons of the olefine, phenylene, or naphthalene series.

Ethylene-diamine, $NH_2CH_2 \cdot CH_2NH_2$

Ethylene-diamine is formed by the reaction of ethylene chloride or bromide and alcoholic ammonia at 100–120° C. It is a viscous volatile liquid, with a slight ammoniacal odor, sp. gr. .902 at 15° C., boiling 117°, easily soluble in water but insoluble in ether. It dissolves albumen and fibin, and is employed in medicine as an adjuvant to the treatment of diphtheria.

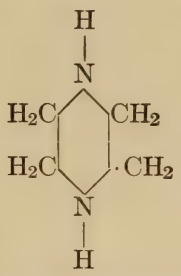
It forms with mercuric sulphate a white crystalline substance known as sublamine, which is soluble in water and glycerin and is used instead of mercuric chloride in syphilis, gynecological practice, and as a vaginal douche.

A solution of silver phosphate in an aqueous solution of ethylene-diamine is called Argentamine, and is used as an antiseptic or astringent in gynecological and ophthalmic practice.

An aqueous solution containing 25 per cent ethylene diamine and 25 per cent cresol is used as a bactericide. Kresamine is a product of this type.

Diethylene-diamine—Piperazine, $C_4H_{10}N_2$

Piperazine is a well-defined base having the composition



It forms colorless, lustrous, tabular crystals, hygroscopic, which melt at 44° C. (104–107° when anhydrous and boils at 145°). It is extremely soluble in water, forming strongly alkaline but non-caustic solutions. which dissolve carbon dioxide. It is not so readily soluble in alcohol. It is volatile. It forms soluble salts with acids, and with uric acid it forms a very soluble salt (in 50 parts of water; lithium urate requires 368 parts of water). It is not affected by chromic acid, but is slowly oxidized by potassium permanganate.

In aqueous solution it gives a characteristic scarlet-red precipitate with potassium-bismuth iodide, a white precipitate with Nessler's reagent, and is precipitated light blue by copper sulphate, white by mercuric chloride, lemon yellow (crystalline) by picric acid and grayish by tannic acid.

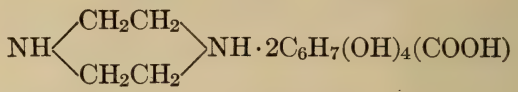
Piperazine forms a series of hydrates containing from one to six molecules of water, the latter being the most readily obtained.

The picrate is very insoluble in water and is obtained by simply adding an excess of a solution of the reagent. The reaction may be used as a means of estimating piperazine, and the details are the same as for determination of antipyrin by the same reagent.

When sodium nitrite is added to a solution of piperazine in dilute hydrochloric acid, and the mixture warmed, a dinitrosopiperazine separates which, on recrystallization from boiling water, forms yellowish plates melting 158°. It gives a deep blue color after some minutes with a solution of phenol in sulphuric acid.

Piperazine is used in gout, for the relief of irritation of the bladder, rheumatism, renal colic, and for the prevention of the formation of renal and vesical calculi.

Sidonal—Piperazine Quinate



the normal salt of piperazine and quinic acid.

It forms a white, crystalline powder, melting at 168 to 171° C., and having a faint acid taste and reaction. It is very soluble in water and forms salts on mixing the aqueous solutions with solution of alkali carbonates and evaporating to dryness.

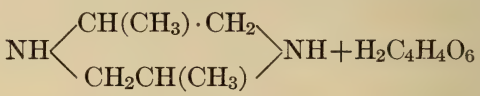
It responds to tests for piperazine (precipitate with potassium-bismuth iodide, etc.) and quinic acid.

Sidonal is used as a uric acid solvent in gout, neurasthenia, etc.

Dimethyl Piperazine—Lupetazin, $NH(C_2H_3 \cdot CH_3)_2NH$

Lupetazin is a colorless oily liquid boiling 153–158°, the base of lycetol. It gives precipitates with iodin, picric acid, and bromin water, but not with Mayer's reagent.

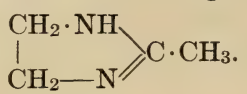
Lycetol—Dimethyl Piperazine Tartrate



It is a white, odorless powder, melting at 250° C., anhydrous, but slightly hygroscopic. It is soluble in water, forming agreeably acidulous solutions.

Ethylene-ethenyl-diamine—Lysidine

Lysidine is an hygroscopic, reddish-white crystalline substance with a peculiar odor resembling coniin and having the composition

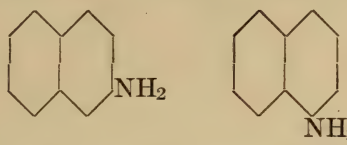


It dissolves easily in water and is used for the same purposes as piperazine.

It melts 100–106°, very soluble in alcohol, somewhat in chloroform, but insoluble in ether. It gives precipitates with the general reagents for alkaloids, and forms a soluble urate.

Naphthylamines, $C_{10}H_7NH_2$

Naphthylamine occurs in two forms, the alpha and beta.



The alpha melts 30°, boils 300° C., soluble in alcohol and ether. The beta melts 112°, boils 294° C., soluble in alcohol, ether, slightly in water.

Thermin—Tetrahydrobetanaphthylamine Hydrochloride, $C_{10}H_{11}NH_2 \cdot HCl$

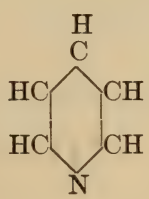
Thermin forms colorless to reddish-white crystals, melting 237° C., soluble in water and alcohol. It is used as a mydriatic, and to increase the bodily temperature.

Pyridin

The nitrogenous bodies with the nitrogen atom in a closed complex are usually derivatives of pyridin, quinolin, or acridin. The plant alkaloids are generally derivatives of the first two.

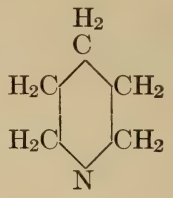
Pyridin, C_5H_5N, occurs in bone oil or coal tar. When pure it is a colorless, mobile liquid with a pungent characteristic odor, boiling 115° and miscible with water in all proportions. It is a strong base, turning red litmus blue and combining with acids to form crystalline salts. The platinochloride crystallizes in orange-yellow needles readily soluble in water, but on boiling, a very sparingly soluble yellow salt separates. If pyridin or its homologues are treated with methyl iodide, a methiodide is produced, and if this is then subjected to the action of heat in presence of potassium hydroxide a very pungent and disagreeable odor is evolved. It does not give the carbylamine reaction nor does it react with nitrous acid.

Pyridin has the structure



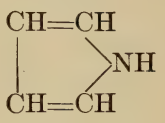
It is unsaturated, but the positions of unsaturation are not as yet satisfactorily established.

Piperidin obtained by boiling piperin with alkalies, is hexahydropyridin



a colorless liquid boiling 106° with a penetrating odor like pepper.

Pyrrole



Pyrrole and two isomeric methyl pyrroles, are associates of the pyridin bases in coal tar and bone oil. Pyrrole is a colorless pungent-tasting liquid with a chloroform-like odor, sp. gr. .9669 at 20°, boiling 130–131°. It is a weak base, dissolving in acids, and is indifferent to alkalies. It is soluble in alcohol and ether, but almost insoluble in water. It forms an unstable red picrate, melting 71°, and a grayish-brown tetraiodo compound melting between 140–150°.

Pyrrole turns brown on exposure to the air. Heating with acid gives pyrrole red, and its vapor reddens a piece of pine wood moistened with hydrochloric acid. A solution of alloxan on boiling with a small quantity of pyrrole turns blue, changing to red on cooling, and to green and blue on addition of alkali.

If pyrrole is added to a weak solution of isatin in water, acidulated with sulphuric acid and cooled to 5°, an indigo blue substance is obtained, which is soluble in concentrated sulphuric acid to a blue to bluish-black solution.

A solution of phenanthraquinone in acetic acid on treatment with pyrrole and acetic acid yields a brown precipitate soluble in chloroform with a violet-red color. An aqueous solution of benzoquinone when treated with pyrrole and dilute sulphuric acid yields a dark-green precipitate.

Iodol—Tetraiodo Pyrrole, C_4I_4NH

Iodol is a grayish-brown powder prepared by the action of iodin in potassium iodide on a solution of pyrrole in the presence of alkali. It

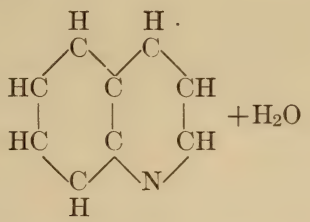
has a faint odor, and on heating is decomposed without melting between 140–150°. It is only slightly soluble in water, but dissolves in the ordinary organic solvents and in acids. It is turned black by hydrochloric acid, and forms an addition compound with eucalyptol, melting with decomposition at 112°. With sulphuric acid it gives a green color changing to violet, and on warming an alcoholic solution with nitric acid a bright-red color appears.

Iodol is valuable chiefly as an antiseptic and alterative, and is used in syphilis, scrofula, etc., as a substitute for potassium iodide. Locally it is employed as a spray for throat affections, and as an ointment or powder or with collodion in chancre, chronic ulcers, and other suppurative conditions.

A compound of iodol and egg albumen is recommended for internal administration. It is a yellow, tasteless, and odorless powder, soluble only in dilute alkalies.

Quinolin and its Derivatives

Quinolin, C_9H_7N, and its isomer, isoquinolin, occur in bone oil and coal tar, but for commercial purposes quinolin is prepared synthetically by Skraup's reaction. Anilin and glycerol are heated with a dehydrating agent such as sulphuric acid and an oxidizing agent such as nitrobenzol. In the reaction it is probable that acrolein is first formed, which then condenses with anilin, forming acrylanilin, and the latter under the oxidizing action of nitrobenzol loses two atoms of hydrogen and is converted to quinolin.



Derivatives of quinolin may be obtained by Skraup's reaction, using derivatives or homologues of anilin.

Quinolin is a colorless highly refractive oil, sp. gr. 1.095 at 20°, boiling 239° C., the commercial boils 230–234°, with a peculiar characteristic odor. It is sparingly soluble in water, but dissolves freely in dilute acids, forming well-defined salts of the composition $X \cdot HCl$. It forms double salts with hydrogen platinic chloride and with potassium bichromate. The latter is sparingly soluble in water and may be obtained on adding potassium bichromate to a solution of the hydrochloride; it melts at 164–167° C.

Isoquinolin is a solid melting 22°, boiling 241° C.

It has a faint odor resembling benzaldehyde.

Quinolin is quite soluble in hot water, but only slightly in cold water. It dissolves easily in all of the ordinary organic solvents and acids. From acid solutions or neutral solutions of its salts quinolin is completely displaced by alkalies, and may be shaken out with ether and recovered.

It is precipitated by iodin, potassium mercuric iodide, phosphomolybdic acid, picric acid, and potassium ferrocyanide in acid solution. The picrate forms bright-yellow needles melting 205°. The platinochloride may be crystallized from hot dilute hydrochloric acid, in yellow needles containing $2H_2O$, melting 225°, and from hot water in small needles with $1H_2O$, melting 218° C. Quinolin also forms soluble salts with acids, the hydrochloride, bisulphate, salicylate, and tartrate. The thiocyanate is used medicinally and the double salt of this acid with bismuth is marketed under the name "Crurin."

Quinolin gives no characteristic color reactions with nitric acid or sulphuric acid or oxidizing agents. The tests of special value for its identification are its precipitation reactions and the melting-points of its purified crystalline salts.

Quinolin and its salts are used in medicine for their antiseptic and antipyretic properties. It is used as a mouth wash and gargle, especially in diphtheria, as an intestinal antiseptic in dysentery, and for irrigating purposes in venereal diseases. It also has a wide use as a vaginal douche. The tartrate is given for intermittent fever.

If it is desired to determine the amount of quinolin in a salt or its solution, the base should be liberated with alkali, shaken out with ether, the ether solution washed, shaken out with a known volume of standard acid, and after separating the acid the excess can be titrated with standard alkali, using methyl red as an indicator. One mil N/10 $H_2SO_4 = .004619$ gram quinolin.

Crurin—Quinolin-Bismuth Sulphocyanate, $(C_9H_7N \cdot HCSN)_3Bi(SCN)_3$

It is a fine, brick-red, crystalline powder, with a slight odor of quinolin, insoluble in alcohol and ether, but soluble in acetone and slightly so in pure glycerin. It is decomposed by water with formation, it is stated, of soluble quinolin sulphocyanate, free sulphocyanic acid, and insoluble basic bismuth sulphocyanate or bismuth hydroxide.

When crurin is decomposed by water there is formed an insoluble yellow compound and a solution which responds to tests for sulphocyanate in that it yields a deep-red color with ferric chloride and a white precipitate with silver nitrate solution, and to tests for quinolin, in that treatment with iodin in potassium iodide solution yields a reddish-brown precipi-

tate insoluble in hydrochloric acid; with picric acid solution it yields a yellow precipitate; with potassium ferrocyanide solution a green precipitate is formed, and with potassium mercuric iodide solution it yields a reddish-yellow precipitate, which dissolves on heating. The yellow insoluble compound, when treated with potassium iodide solution, becomes orange colored, and it responds to tests for bismuth.

Crurin treated with dilute nitric acid dissolves with formation of a solution from which bismuth can be separated by precipitation with hydrogen sulphide for quantitative estimation and in which the sulphocyanate content can be determined by titration with standardized silver nitrate solution.

It is useful as a local application for gonorrhea. It is also used in the treatment of ulcers of the leg.

Quinoiodin or Chinoiodin is a chlorin-iodin addition product of quinoline, C_9H_7NICl. It is a yellow powder soluble in alcohol and insoluble in water, used as an antiseptic in dusting powders and petrolatum ointments.

Iodolin—Quinolin Chloriodomethylchloride, $C_9H_7NCH_3ClCH$

Iodolin is a yellow powder soluble in alcohol and slightly in water, also used as an antiseptic.

Quinolin gives rise to a number of important derivatives.

Tetrahydroquinolin, $C_6H_4\begin{cases}CH\cdot CH_2\\ \quad\quad |\\ NH\cdot CH_2\end{cases}$, boils 245–251° C., soluble in alcohol and ether and slightly in water and gives a platinochloride which melts 200°. This is a secondary base, yielding nitrosamin and capable of alkylation. It has strong antiseptic properties.

Tetrahydroisoquinolin boils 232° and is soluble in alcohol, water, and ether.

8-Hydroxyquinolin, $OH\cdot C_9H_6N$

This is the base of Chinosol, a widely advertised antiseptic. It has a characteristic saffron-like odor, melts 75–76°, is volatile with steam, and sublimes slowly at the ordinary temperature. It is soluble with difficulty in ether and cold water, but dissolves readily in chloroform, alcohol, acids, and dilute alkalies. Its acid and alkaline solutions are yellow, and a colorless alcoholic solution turns yellow when water is added. Its aqueous solution gives a green color with ferric chloride, and a red color followed by a black precipitate with ferrous sulphate.

The hydroxyquinolin sulphonic acids are employed medicinally.

Vioform—Iodochloroxyquinolin—Nioform

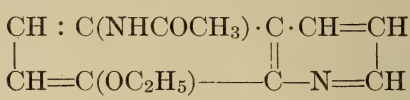
Vioform is iodo-chlor-hydroxy-quinolin, $C_9H_4N \cdot OH \cdot I \cdot Cl$.

It is a voluminous, greenish-yellow powder; crystallizing from glacial acetic acid in needles melting at 177 to 178° C., practically odorless, and insoluble in water, and slightly soluble in alcohol.

Vioform contains 41.57 per cent of iodin—it gives a green coloration with Millon's reagent or when the alcoholic solution is treated with ferric chloride solution. It dissolves with a brown color in concentrated sulphuric acid and the solution evolves iodin on warming. If this solution, after driving off the iodin, is diluted with water, chlorine can be demostrated by the usual test with silver nitrate. If a solution of vioform in chloroform is shaken with nitric acid, the chloroform acquires a violet-red color, and the nitric acid becomes somewhat yellow.

It is antiseptic, and hemostatic.

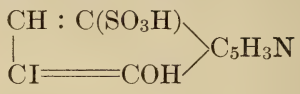
Analgen—5-acetylamino-8-ethyoxyquinolin



This substance forms colorless crystals, melting 155°, readily soluble in alcohol, slightly in water, acidified solution yellowish red.

The corresponding benzoyl compound is called Benzanalgen, Quinalgen, or Laborin, a white, tasteless crystalline powder melting 208°, readily soluble in dilute acids.

Loretin—7 iodo-8-hydroxyquinolin-5 Sulphonic Acid



Loretin is a colorless, tasteless, reddish-yellow crystalline powder which darkens on heating and evolves iodin at 260°. It is soluble in alcohol and water and in hot concentrated sulphuric acid without decomposition.

The sodium salt is used as an antiseptic and is sometimes dispensed in combination with bismuth subnitrate. Loretin is also combined with iodoform, starch, talc, and magnesia, and is a component of many pencils, gauzes, etc., used in venereal diseases and for skin affections. The soluble form is sometimes called " Griserin."

Argentol or silver quinaseptolate is the silver salt of hydroxyquinolin sulphonic acid. It is a yellow powder, soluble with difficulty in water.

Diaptherin is a combination of 8-hydroxy quinolin and *p*-phenol sulphonic acid, green crystals, melting 85°, moderately soluble in water, but with difficulty in alcohol. Ferric chloride gives a bluish-green color which becomes yellow on adding hydrochloric acid. It is used for rheumatism and as an antiseptic.

Diapthol—7-hydroxyquinolin meta Sulphonic Acid

Yellowish-white crystals melting 295°, fairly soluble in water and useful as an urinary antiseptic.

Atophan

Atophan is 2-phenyl-quinolin-4-carboxyic acid,

$$C_9H_5N \cdot C_6H_5 \cdot COOH \cdot 2 : 4$$

Atophan crystallizes in small colorless needles, melting at 208–209° C. It is insoluble in water, but readily soluble in alkalies, hot alcohol, and boiling glacial acetic acid. It has a slightly bitter taste.

Atophan is used in the treatment of gout and rheumatic conditions,

Novatophan

Novatophan is ethyl 6-methyl-2-phenyl-quinolin-4-carboxylate, $CH_3 \cdot C_9H_4N \cdot C_6H_5COOC_2H_5$, 6 : 2 : 4, the ethyl ester of paratophan, (6-methyl-2-phenyl-2-quinolin-4-carboxylic acid).

It is a slightly yellow, odorless, and tasteless crystalline powder, melting at 76°. It is insoluble in water, but readily soluble in alkalies, hot alcohol, and strong acids.

If 0.1 to 0.2 gram novatophan is boiled for a short time with 0.5 mil sodium hydroxide solution, then 5 mils iodin test solution added and again heated, the odor of iodoform will be apparent.

When dissolved in concentrated sulphuric acid, a light-yellow solution results which on the addition of bromin water yields a reddish-yellow precipitate.

On adding ferric chloride to an alcoholic solution of novatophan a yellow, not a brown color, is produced.

Paratophan

Paratophan is methyl-atophan, 6-methyl-2-phenyl-quinolin-4-carboxylic acid, $CH_3C_9H_4N \cdot C_6H_5 \cdot COOH$, 6 : 2 : 4.

It is a yellow crystalline powder melting at 228°, soluble in alcohol, ether, chloroform, and alkalies, but insoluble in water. It has a slightly bitter taste and a faint odor.

When dissolved in concentrated sulphuric acid a light-yellow solution results, which yields a light-yellow precipitate on the addition of bromin water.

If ferric chloride solution is added to an alcoholic solution of paratophan, a brown color is produced.

If paratophan is heated above its melting-point carbon dioxide is liberated and methyl-phenyl-quinoline, $CH_3C_9H_5N \cdot C_6H_5$, melting at 68° is produced.

Thalline—6-methoxytetrahydroquinolin

Thalline is prepared by heating *p*-aminoanisole and *p*-nitroanisole with glycerol and sulphuric acid and subsequent reduction. The free base crystallizes in colorless prisms, melting 42°, boiling 283°, pungent, sparingly soluble in water but readily in alcohol, ether, chloroform, and benzol.

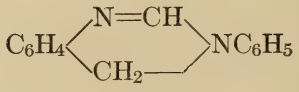
Thalline is usually marketed as the sulphate which is readily soluble in water. An aqueous solution gives precipitates with the general alkaloidal precipitants and alkalies; ferric chloride added to very dilute solutions produces a yellow color, changing to emerald green and finally passing to red; and a green color may also be obtained with gold chloride, mercuric chloride, silver nitrate, chlorine water, and in acid solution with bleaching powder and potassium ferrocyanide. β-naphthaquinone in aqueous solution treated with a solution of thalline sulphate and a drop or two of sodium hydroxide yields a red color, made more brilliant by nitric acid and soluble in ether or chloroform.

The free base dissolves in sulphuric acid without color, but the addition of nitric acid causes a deep-red color changing to a yellowish red. Sulphuric acid containing sugar produces a red color.

The sulphate is used in yellow fever. An addition compound of thalline and iodin is used for carcinoma.

Orexine—3-phenyl-3, 4-dihydroquinazolin

The base of orexine is a derivative of a quinazoline and is obtained by treating formanilid sodium with *o*-nitrobenzyl chloride and reducing the ortho-nitrobenzylformanilid,



Orexine is the hydrochloride of the base, but the term is applied indiscriminately to the base and the hydrochloride, for there is a substance called orexine tannate which is claimed to be a tannate of the base.

The base is soluble in alcohol, ether, and chloroform, but dissolves in acids and is thrown out of acid solution by alkalies. A solution of the base is precipitated by mercuric chloride, the deposit dissolves in hot water, but crystallizes out on cooling. The precipitate with potassium bichromate has similar properties. Bromin water is decolorized, and a yellow amorphous precipitate thrown down; tannin produces a precipitate and permanganate undergoes reduction. The solid substance when heated with zinc dust evolves phenyl-isocyanide, and the residue, on treatment with hydrochloric acid, filtering and adding calcium hypochlorite solution, gives the blue color characteristic of anilin. A solution of the base in concentrated sulphuric acid is colored green by nitric acid, a reddish color appearing on the edges.

Orexine hydrochloride crystallizes with 2 molecules of water,

$$C_{14}H_{12}N_2HCl+2H_2O$$

It produces violent sneezing, and in medicine is used as a tonic and stomachic.

The tannate is almost insoluble in water, but dissolves in dilute hydrochloric acid. It gives the characteristic reaction of a tannate, and the base may be precipitated by alkali from a solution in 30 per cent acetic acid.

Phenylene-diamines—Diaminobenzenes, $C_6H_4(NH_2)_2$

There are three modifications, ortho, melting 102–103°; meta, melting 63°; para, melting 140°; boiling respectively 252°, 287°, 267°. Sodium nitrite, added to neutral aqueous solutions, give with *o* separation of amino-azo-phenylene as a colorless oily liquid, with *m*-yellow or brown color or precipitate of triamino-azobenzene, with *p*- no color. The meta is easily removed from alkaline solutions by ether. The hydrochloride is a well-defined salt, known commercially as Lentin.

The meta-compound is used in acute bowel trouble where an antiseptic is required.

The para is used as a hair dye. A solution of the base in weak potassium hydroxide when mixed with hydrogen peroxide develops a black color, and with ferric chloride a brown.

In case of poisoning caused by hair dyes, this substance or a diamino toluene may be suspected.

Paraphenylene diamine is prepared directly from acetanilid by nitration and subsequent reduction. This fact should be borne in mind by the control chemist who may be called upon to testify in cases involving the analysis of a preparation containing the base. It is of course questionable whether a hair dye is a medicine or a drug, being more properly a cosmetic, which is not subject to the drug act as it is at present interpreted.

Methylene Blue, $C_{16}H_{18}N_3SCl$. Tetramethylthionine

Methylene blue is an oxidation product of dimethyl para-phenylenediamine in hydrogen sulphide solution. The medicinal product should be free from zinc chloride. It is a dark-green or red-brown bronzy powder, readily soluble in water to a deep-blue solution, and is removable from an alkaline solution with ether. It dyes cotton mordanted with tannin a blue color which is fast to light and soap.

Methylene blue has attained its greatest reputation as a remedy for gonorrhea, and is usually dispensed in capsules or pills. It will be found by itself and in combination with copaiba, and oils of santalwood and cinnamon, methyl salicylate, and haarlem oil.

It is the ingredient of kidney remedies advertised to the laity, the literature of which admonishes the patient to observe the urine after taking, and if it acquires a greenish color he may know the remedy is doing its work. These remedies, usually in the pill form, may contain in addition to methylene blue, buchu, juniper, potassium acetate or nitrate, copaiba, cubeb, methyl salicylate, aloes, extracts of Eupatorium, triticum, Pichi, Chondrodendron tormentosum, Hydrangea, cornsilk, and others.

Toluylene-diamines—Diaminotoluenes, $C_6H_3(CH_3)(NH_2)_2$

The substances occur in two types, the alpha and beta. The former is the ortho-para modification (1–2–4), melting 99°, and the latter the meta-para (1–3–4). They closely resemble the phenylene diamines.

Comparative reactions of these two substances in neutral or slightly acid solutions have been reported as follows:

Ferric Chloride. Alpha—No change at first, orange on long standing.
Beta—Wine-red color.

Potassium Bichromate. Alpha—Yellowish-brown color.
Beta—Reddish-brown precipitate.

Potassium Ferricyanide. Alpha—Olive-green crystalline plates.
Beta—Dark-red color.

Bromin Water. Alpha—Yellowish-white precipitate.
Beta—Brown flocks, magenta-red solution.

Potassium Nitrite. Alpha—Golden-brown color, dilute. Brown precipitate when concentrated.
Beta—Salmon-red precipitate.

Bleaching Powder Solution. Alpha—Reddish-brown color, light brownish-yellow precipitate.
Beta—Dark-red color. Olive-green precipitate.

These bodies are used in hair dyes. The treatment consists of either a solution of the diamine in alkali; or an amount of the crystalline substance sufficient for an application and another bottle containing a reagent which, when mixed with it, will bring out the requisite color.

AMIDES

Amides may be considered as substituted ammonias in which the hydrogen has been replaced by an acid radicle. There are three classes, primary, secondary, and tertiary.

$$\begin{matrix} H \\ N—COCH_3 \\ H \end{matrix} \qquad HN=(COCH_3)_2 \qquad N(COCH_3)_3$$

Acetamide, CH_3CONH_2, may be obtained by the interreaction of acetyl chloride or acetic anhydride with ammonia, or by distilling ammonium acetate in a stream of dry ammonia gas. It crystallizes in colorless, deliquescent needles, melting 80–82° and boiling 222° C. It is almost odorless when pure, but as usually found has a strong mousy odor. It dissolves in water and alcohol and when heated with mineral acids or alkalies is decomposed into acetic acid and ammonia or their salts. On distillation with phosphoric anhydride it loses a molecule of water and is converted into methyl cyanide or acenitrile,

$$CH_3CONH_2 = CH_3CN + H_2O.$$

Neuronal—Diethylbromacetamide, $Br(C_2H_5)_2CONH_2$

Neuronal is a white crystalline powder, with a camphoraceous odor and a bitter, cooling taste. It melts 66–67° C. and is somewhat soluble in water, readily in alcohol and ether. It is used as an hypnotic.

When heated with dilute sodium hydroxide, sodium bromide and cyanide are produced and diethylketone set free.

Salicylamide, $C_6H_4(OH)CONH_2$

Salicylamide is a colorless crystalline substance, melting 138° C., soluble in alcohol, ether, chloroform, and slightly in water.

It is used as a remedy for rheumatism and fevers and has antiseptic properties like salicylic acid, which it resembles in those reactions which are characteristic of the phenolic group.

Valeric Acid Diethylamide, $CH_3CH_2CH_2CH_2CONH_2$

This body, known as Valyl, is a colorless liquid with a methyl-like odor, boiling 210° C., soluble in alcohol, ether and somewhat in water.

It has hypnotic and antineuralgic properties, and is employed in nervous troubles.

Urea and Its Derivatives

Urea, $C(=O)(NH_2)_2$, or carbamide, is the amide of the dibasic carbonic acid, $C(=O)(OH)_2$. It is a substance of great importance in physiological chemistry, and methods for its detection and determination have been the subject of a vast amount of research. It is used in a limited way in medicine, but some of its derivatives have an extended use and are of considerable interest to the drug chemist.

Urea is used in tuberculosis and as a diuretic. In renal calculus it is sometimes given in comparatively large doses.

Urea forms transparent, colorless, somewhat hygroscopic prisms, odorless, or with a faint odor suggestive of urine, melting at 132° and decomposing at 150–160° with evolution of ammonia and formation of biuret. It may be distilled *in vacuo* at 135° C.

It is very soluble in alcohol and cold water and much less in hot water. It is but slightly soluble in ether, and the other organic solvents have little or no action.

On fusion with caustic alkalies, ammonia is evolved and a carbonate is formed. On heating with strong mineral acid carbon dioxide is given off and a salt of ammonia produced. Pure concentrated nitric acid combines with urea without decomposing it, but if nitrous acid is present, nitrogen and carbon dioxide are evolved.

Urea forms salts which are dissociated by water, the nitrate and oxalate are easy to prepare, and the latter is but sparingly soluble in cold water.

Urea is not precipitated by the usual alkaloidal reagents, nor does it give color tests with the oxidizing agents. When heated at 160° for some time, the residue dissolved in water and made slightly alkaline with sodium hydroxide, the addition of a dilute solution of cupric sulphate will produce a violet or red color. This is known as the biuret test. It is precipitated by mercuric nitrate from a solution free from chlorides and it is not precipitated by mercuric chloride. The mercuric nitrate

compound may be used to good advantage in the purification of urea, because it can be separated from the solution, washed and decomposed by hydrogen sulphide with liberation of the base.

Adalin

Adalin, $C(C_2H_5)_2Br \cdot CONH \cdot CONH_2$, is bromdiethyl-acetyl-carbamide.

It is an almost colorless and odorless crystalline powder, with a melting-point of 116° C., which dissolves readily in alcohol as well as in the other ordinary organic solvents. It is difficultly soluble in water.

It is used as a sedative and mild hypnotic.

Bromural

Bromural, $(CH_3 \cdot CH(CH_3)CHBr \cdot CO)HN \cdot CO \cdot NH_2$, is 2-mono-brom-isovaleryl-urea.

It forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol, and alkalies, but less readily in cold water. It sublimes on heating and melts in the neighborhood of 145° C.

Bromural can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromin may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for a bromide with silver nitrate solution. On heating the alcoholic solution of bromural with sodium ethylate for several hours on the water-bath, sodium bromide will precipitate. If this is filtered off and the filtrate evaporated, a crystalline mass will remain which can be recrystallized from water. This is dimethylacrylic acid, melting at 280° C.

If 1 gram bromural is boiled for about one minute with 10 per cent solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid is then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oily fluid, 1-brom-isovaleric acid, which has the specific odor of valeric acid, will remain.

The biuret reaction cannot be obtained. On melting bromural and adding concentrated sodium hydroxide solution and copper sulphate, no color reaction will take place.

Bromural is a nerve sedative.

Thiosinamine—Allyl Sulphocarbamide—Allyl Thiourea—Rhodaline

Thiosinamine is allyl-thio-urea, $(NH_2) \cdot CS \cdot NHCH_2 \cdot CH : CH_2$.

It forms colorless crystals, having a slight alliaceous odor and bitter taste and melting at 74° C. It is moderately soluble in water, but is decomposed by this solvent. It is soluble in about 3 parts of alcohol and readily soluble in ether.

It is used by hypodermic injection in lupus, chronic glandular tumors, and by mouth in stricture, corneal opacity, chronic deafness.

Fibrolysin

Fibrolysin, $(NH_2 \cdot CS \cdot NHCH_2 \cdot CH : CH_2) + C_6H_4(OH)(COONa)$, is a sterilized solution of a double salt of thiosinamine and sodium salicylate containing 15 per cent of the double salt.

The tests are those of thiosinamine and sodium salicylate.

Maretin—Metatolylhydrazine Carbaminate, $C_6H_4 \cdot CH_3NHNHCONH_2$

Maretin forms colorless, lustrous crystals, melting 183–184°, somewhat soluble in alcohol, but only slightly in ether, chloroform, and water. It is an antipyretic.

Ethyl Carbamate—Urethane

When urea or its nitrate are heated to 100° C. with alcohol, ethyl carbamate, $C{=}O(OC_2H_5)(NH_2)$, is formed. It is a colorless crystalline substance, with a faint peculiar odor and a saline taste, melting 48–50° and boiling 180° C. It is readily soluble in water, alcohol, ether, chloroform, and glycerin. On warming with concentrated sulphuric acid, carbon dioxide is evolved and alcohol and ammonium bisulphate remain in solution. On warming with concentrated alkali, ammonia gas is given off. An aqueous solution treated with sodium carbonate and a little iodin, will deposit iodoform on warming. Its aqueous solution gives no precipitate with nitric acid, mercuric nitrate, or oxalic acid.

Urethane is used as a sedative, hypnotic, and antispasmodic, and will be found in remedies for insomnia, nervousness, and tetanic poisons.

Urethane forms a compound with chloral having the composition $CCl_3CH(OH)(NH)COOC_2H_5$, and known as chloralurethane, furalium, ural, or uraline. It melts 103° C. and is soluble in alcohol and ether. This substance is also used as an hypnotic.

Ethylidene urethane, $CH_3CH(CO(NH)OC_2H_5)_2$, is a crystalline body melting 125–126° resulting from the action of hydrochloric acid on a solution of urethane in acetaldehyde.

Phenyl urethane, $CO(OC_2H_5)(NHC_6H_5)$, is closely allied to urethane. It is called Euphorin. The product is prepared by the action of anilin on the ethyl ester of chloroformic acid. It occurs in the form of colorless

needles or a white powder with a faint odor and a clove-like taste, melting 50–51°. It is but slightly soluble in water, but soluble in dilute alcohol, strong alcohol and ether.

It is used internally for rheumatism, sciatica, and headache, and externally as a dusting powder for venereal sores, skin diseases, etc.

Hedonal—Methylpropylcarbinol Urethane

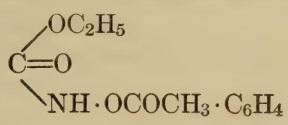
Hedonal is pentan-2-ol urethane, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH(CH_3)O \cdot CO \cdot NH_2$.

It is a white, crystalline powder, having a faint aromatic odor and taste, melting at 74° C., and boiling at 215° C. It dissolves in 120 parts of water at 37° C. but is more soluble at higher temperatures and is readily soluble in alcohol, ether, chloroform, and other organic solvents. It is readily volatilized with the vapors of water or alcohol, and when boiled with alkalies is split up into its constituents, methylpropylcarbinol, ammonia, and carbon dioxide.

On boiling with dilute sodium hydroxide, ammonia is evolved and recognized by the odor and the usual reactions; if then an aqueous solution of iodin in potassium iodide is added, and the mixture allowed to cool, the odor of iodoform derived from the alcohol is distinctly manifested.

Hedonal appears to have a greater hypnotic effect than ethyl carbamate.

Neurodin—Acetylparaoxyphenylurethane

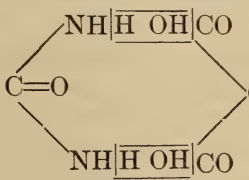


Neurodin may be considered as a derivative of amido phenol as well as of urea. It forms colorless crystals, melting 87° C., which are slightly soluble in water.

It is used as an antipyretic and antineuralgic.

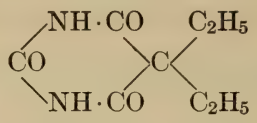
Thermodin is claimed to be acetyl paraethyoxyphenyurethane, hence it should stand in close relationship to the last-named substance.

Barbituric Acid and Its Derivatives

When urea and malonic acid react under proper conditions, barbituric acid results,  . In this body the central hydrogen atoms have acid properties.

Veronal—Diethyl Malonyl Urea

Veronal is diethyl-barbituric acid, 2, 4, 6-trioxy-5-diethyl pyramidin,



a ureide derived from diethylmalonic acid, $COOH \cdot C(C_2H_5)_2 \cdot COOH$, and urea, $CO(NH_2)_2$.

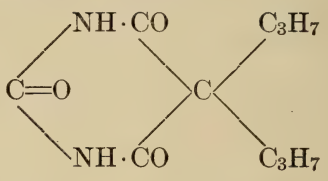
It is a white, crystalline powder, melting at about 188–191° C., subliming on heating, odorless and faintly bitter. It is soluble in about 150 parts of cold water and in about 12 parts of boiling water. It is quite soluble in ether, acetone and ethyl acetate; also slightly soluble in chloroform, petroleum benzine, acetic acid, and amyl alcohol. It forms salts with alkalies which are soluble in water.

Prolonged heating with sodium carbonate solution liberates ammonia. Denigè's reagent produces a white precipitate; Millon's reagent produces in solution acidulated with nitric acid a precipitate soluble in excess of the reagent.

When added to potassium hydroxide, fused in a nickel crucible, and heated for two minutes, the cold mass on dissolving in water should give a blue precipitate with ferrous sulphate; on adding excess of acid and shaking with ether, an oily mass is extracted, having the odor of rancid butter, soluble in water, and giving a wine-red color with ferric chloride.

A so-called salt of the above ureide with sodium is marketed as Veronal-sodium, as Medinal and probably other designations. It is soluble in 5 parts of water. Veronal is an hypnotic.

Proponal—Dipropylmalonylurea

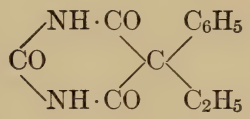


Proponal is closely allied to veronal, dipropylmalonic acid being used in the synthesis instead of the diethyl compound. It forms colorless crystals slightly soluble in cold water, more readily in hot, and easily in alcohol, ether, chloroform and alkalies. It melts 145° C.

It is used for the same purposes as veronal.

Luminal—Phenyl-ethyl-barbituric Acid—Phenyl-ethyl-malonyl-urea

Luminal is phenyl-ethyl-barbituric acid, 2, 4, 6-trioxy-5-phenyl-ethyl pyramidin,



Luminal is a white, odorless, slightly bitter powder. It is almost insoluble in cold water, slightly soluble in hot water and readily soluble in alcohol, ether, and chloroform, and in alkaline solutions. It crystallizes from boiling water to lustrous leaflets, and is precipitated unchanged by acids from its alkaline solutions. It melts at 173–174° C.

If about 0.3 gram is shaken for a short time with 1 mil of normal sodium hydroxide and 5 mils of water, and the mixture filtered, the filtrate will yield white precipitates on the addition of mercuric chloride and of silver nitrate solutions.

If about1 gram is boiled for five minutes in 10 mils of a 50 per cent solution of sodium hydroxide, ammonia will be evolved.

If about 1 gram is dissolved in 5 mils of normal sodium hydroxide and the solution heated for four hours on a boiling water-bath, the evaporated water being replaced, crystals of pheny-acetyl-urea will separate on cooling. When recrystallized from dilute alcohol these crystals melt at 147° C.

Luminal is used as an hypnotic in nervous insomnia and conditions of excitement of the nervous system.

Adrenalin—Epinephrin

The suprarenal glands of sheep and other animals contain a basic substance which has a strong physiological action causing a rise in the blood pressure, and is used in hemorrhage, catarrhal, and congestive conditions. The blood pressure raising principle has been separated and purified and is now a commercial article being sold under several names, adnephrin, adrenalin, adrin, epinephrin, supracapsulin, suprarenalin, etc. Some controversy has arisen as to the name which was first applied to this substance before its composition was known, but the merits of the case need not be discussed here.

The active principle is usually marketed in a weak solution (1 : 1000) of the hydrochloride, and as it is very unstable, some preservative such as chloretone is added to the solution, and it is further inertized by saturating with carbon dioxide. There is also a large demand for the desiccated glands and their extract.

The active principle is sometimes combined with cocain and with spartein in tablets, it is also formulated with sodium chloride and boric acid in order to yield a non-irritant solution. It is put up in oily mixtures to be used as a nasal spray and in ointments and suppositories. The oily inhalants usually contain alcohol. Its use is extending to complex lotions and ointments, but it is of such an unstable nature that the value in these products is questionable.

Epinephrin is 1, 2-dihydroxy-4[2]-methylamino ethyl-4[1]-ol benzene, $C_6H_3(OH)_2(CHOH \cdot CH_2NHCH_3)$.

It is a finely crystalline white or yellowish powder, odorless and slightly bitter. It melts at 201–207° C., turning brown and decomposing at the higher temperature.

It shows a slightly alkaline reaction to moistened red litmus paper. It is almost insoluble in cold water, more readily in hot water. It is difficultly soluble in alcohol and insoluble in ether. The colorless aqueous solution is easily oxidized on contact with the air, becoming pink, then red, and eventually brown. The base reacts with acids to form salts which are readily soluble in water; it is also soluble in the fixed alkalies, but not in ammonium hydroxide or in solutions of the alkaline carbonates. The following reactions are the most characteristic: The addition of ferric chloride to a solution of the alkaloid produces a beautiful emerald-green color which by careful addition of caustic alkali becomes purple, and then carmine red. Strong acid prevents the reaction with ferric chloride, limiting the change of color to a dirty yellowish-green. It gives a vivid pink color with iodin. The alkaloid reduces silver salts and gold chloride very energetically, and the liquid turns red. A drop of 1 : 10,000 solution instilled into the eye will, within a few seconds, produce a pallor of the conjunctiva.

L-Suprarenin Synthetic

L-suprarenin synthetic is epinephrin produced synthetically according to the method of Stolz and Flaecher.[1]

It is a white, odorless powder nearly insoluble in water, alcohol, and ether. It melts at 211–212°. It has the power of rotating polarized light to the left:

$$(a)\ \frac{19.6^\circ}{D} = -51.4^\circ.$$

It has the chemical and physical properties and physiologic effect of natural epinephrin obtained from suprarenal glands.

Methods for the determination of adrenalin in order to arrive at a

[1] Ztschr. f. physiol. Chem., 58, p. 189.

standard for desiccated suprarenal glands, have been the subject of much study.

Hale and Seidell published a method based on a color comparison with platinic chloride and cobalt chloride, Folin, Cannon, and Denis recommended the use of phosphotungstic acid, and later Seidell substituted gold chloride for platinic chloride in his original method. These procedures in the order of their appearance are included.

Method of Hale and Seidell.[1]—.01 gram of the desiccated gland is treated with 5 mils dilute hydrochloric acid and 5 mils potassium iodate solution 0.2 per cent, heated just to boiling, allowed to stand fifteen minutes, filtered and the color compared with a series of standards. The latter are made up from a mixture of potassium platinic chloride and cobalt chloride solutions, which develop a color similar to that given by epinephrin and potassium iodate and which have been previously standardized against the ash-free active principle. The yellowish extractive matter present in the aqueous solution interferes with the test, but may be obviated by using a small quantity of the sample and not diluting.

Method of O. Folin, W. B. Cannon, and W. Denis.[2]—The glands are extracted with N/10 hydrochloric acid and water, the mixture being finally heated to boiling. After the addition of sodium acetate solution and further boiling, the mixture is diluted with water and filtered or centrifuged to obtain a clear extract. As a rule, 100 mils of extract are obtained from 2 grams of gland. Five mils are put into a 100-mil flask and 1 mil fresh uric acid solution containing .0010 gram of the acid is put into another flask. A special reagent is then made as follows: 100 grams sodium tungstate and 80 mils of 85 per cent phosphoric acid are boiled gently with 750 mils water for two hours and then made up to 1 liter. Two mils of the reagent and 20 mils of saturated sodium carbonate solution are added to each of the 100-mil flasks, allowed to stand for a few minutes, shaken and made up to the mark. The colors of the deep-blue liquids are compared in a Duboscq colorimeter. The amount of epinephrin can be calculated from the fact that it produces three times as much color as an equal weight of uric acid.

Johannesohn used this method for estimating epinephrin in ordinary commercial preparations, but found it inapplicable in the presence of novocain or alypin.

Method of A. Seidell.[3]—0.01 gram of the sample is shaken with 0.005 gram of manganese dioxide and 10 mils water and after standing one hour the mixture is filtered into a test-tube and the color compared with that of a color standard in a tube of similar dimensions. The color

[1] Am. J. Pharm., 83, 551.
[2] J. Biol. Chem., 1913, 13, 472.
[3] J. Biol. Chem., 1913, 15, 197.

standards are prepared from solutions of cobalt chloride 2 per cent (with 1 mil conc. HCl) and gold chloride 0.1 per cent as shown in the following table:

Epinephrin	Color Standard		
	Cobalt Solution	Gold Solution	Water
Gram	Mils	Mils	Mils
.00001	1.15	.70	8.15
.00002	1.85	.95	7.20
.00003	2.40	1.10	6.50
.00004	2.95	1.25	5.80
.00005	3.50	1.30	5.20
.00006	4.05	1.35	4.60
.00008	5.15	1.55	3.30
.00010	6.30	1.75	1.95

The oxidation product of epinephrin which results when a solution of the base is treated with an excess of ammonia, is soluble in amyl alcohol, but does not dissolve in chloroform, ether, or petroleum ether. It gives a bluish-green color with a very dilute solution of potassium ferricyanide containing ferric chloride, and a blue color with an ammoniacal solution of phosphomolybdic acid. It does not respond to the other characteristic reactions for epinephrin according to Venturoli and Gailbrani,[1] who have made a study of the oxy body.

Tyramine

Tyramine is para-hydroxy-phenyl-ethyl-amine hydrochloride

$$OH \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot NH_2 \cdot HCl$$

The base para-hydroxy-phenyl-ethyl-amine was first isolated by Barger from ergot and also prepared synthetically by him by the reduction of para-hydroxy-acetonitrile with sodium in alcoholic solution. It is chemically and physiologically related to epinephrin ($C_6H_3(OH)_2(CHOH \cdot CH_2NHCH_3)$).

Tyramine occurs as an almost white crystalline powder, easily soluble in water, forming a neutral solution.

Taken internally or injected subcutaneously tyramine increases the blood pressure; for this reason it can be used in shock or collapse; it is also claimed to be valuable for producing post-partum contraction of the uterus. It is useless as a local hemostatic.

[1] Giom. Farm. Chim., 1911, 60, 97.

CHAPTER XXI

ANILIDES AND PHENETIDINS

ANILIN, $C_6H_5NH_2$

Anilin is an important substance in the chemistry of medicinal products, but it is seldom used itself as a drug. Its properties are antiseptic. It is one of the intermediary products formed in the quantitative estimation of acetanilid, and it results in the hydrolysis of some closely allied chemicals whose identity it may help to establish. Hence it is advisable to be thoroughly familiar with the properties of anilin and also the analogous compounds, amino phenols, $C_6H_4\begin{matrix}OH\\NH_2\end{matrix}$, which are obtained by the reduction of nitro phenols, while anilin comes from nitro benzol.

The pure substance is colorless, but it becomes yellow or brown on exposure to light and air due to oxidation. It is of oily consistency, sp. gr. 1.0254 at 15° C., solidifying 6°, boiling 184°. It is but slightly soluble in water, but dissolves easily in alcohol, ether, chloroform, acetone, and acid liquids. It is thrown out of an acid solution by excess of alkali, and can be recovered unchanged by shaking with ether. It dissolves sulphur, phosphorus, and colophony, but not caoutchouc nor copal. It combines readily with bromin to form tribromanilin, and the aqueous solution of anilin gives an immediate precipitate if treated with bromin water or bromide-bromate reagent.

Anilin is a strong base, forming well-defined stable salts with acids of the composition of $C_6H_7N \cdot H \cdot R$. A cold aqueous solution of an anilin salt is converted into a salt of diazo benzene when treated with nitrous acid or a nitrite and mineral acid, and on subsequent boiling phenol is produced with evolution of nitrogen.

Anilin gives the well-known and disagreeable carbylamine reaction when warmed with chloroform and potassium hydroxide. With sulphuric acid and manganese dioxide a purple color results, and purplish shades are given under the same conditions in presence of other oxidizing agents. The reactions somewhat simulating those of strychnin. Nitric acid gives a purple color in the cold, changing to indigo blue and then to greenish blue on heating over the steam-bath, then as the reaction becomes more

violent a brownish-black shade develops. The residue gives an aromatic odor with alcoholic potash.

When a small amount of anilin is treated with an aqueous solution of carbolic acid followed by a solution of bleaching powder, yellow streaks, changing to greenish blue, are obtained. If anilin is treated with 2 to 3 drops of dilute solution of bleaching powder 1 in 200, in such a manner that the two liquids do not mix, a purple or blue color will form at the junction of the liquids.

Anilin combines with equivalent amounts of dilute and concentrated acids, except nitric to form salts, and it furthermore yields stable derivatives on treatment with excess of acids and subjecting to higher temperatures, thus with sulphuric acid a series of amino-benzene sulphonic acids, $C_6H_4 \cdot NH_2SO_3OH$, result, and with acetic acid, acetanilid, $C_6H_5NH \cdot COCH_3$, is formed.

Nitric acid, when dilute, converts anilin to nitranilins and when concentrated to quinone and other substances.

If a solution of anilin in concentrated hydrochloric acid 1 in 3 diluted with an equal volume of water is diazotized with sodium nitrite and the diazotized solution saturated with dry sodium chloride and poured off from any undissolved salt, the ice-cold solution, when treated with stannous chloride in concentrated hydrochloric acid, 6 to $2\frac{1}{2}$ (in proportion to the anilin used) will separate out phenylhydrazine hydrochloride after several hours standing.

This reaction is of interest to the drug chemist, from a theoretical point of view, because antipyrin can be prepared from phenylhydrazine. We have thus an anomalous situation in control work for antipyrin, though not an inhibited drug, can be obtained directly from anilin, the base substance of acetanilid, while acetphenetidin, which is not made from anilin at all, but from amino phenol, is classed as a derivative of acetanilid.

Bromamide

Bromamide is the hydrobromide of tribromanilin, $C_6H_4Br_3NHBr$. It forms colorless, odorless, tasteless needles, melting 154–155° C., soluble in chloroform, ether, and hot alcohol, but insoluble in water. It is used as an antipyretic, antineuralgic, and antirheumatic.

Paraiodanilin, $C_6H_4NH_2$ I. 1–4

This a colorless to bluish crystalline substance, melting 60° C., soluble in alcohol, ether, and chloroform. Its hydrochloride is yellowish, soluble in alcohol and slightly in water. It is used as an antiseptic.

The homologues of anilin have similar properties.

There are three toluidines and six xylidines; they are all liquids at the ordinary temperature except para-toluidin. Their identification or determination becomes a matter of moment when one is working with an abnormal specimen of some anilin derivative which is suspected of containing derivatives of its homologues. The acetyl derivatives of some of them are credited with possessing antipyretic properties and may sometimes be substituted for acetanilid.

	Melting-point	Boiling-point	Melting-point of acetyl derivative
Ortho-toluidin.....	below −20°	199.5°	114°
m-toluidin.....	below −13°	197	107
p-toluidin.....	+45°	198	65–66
u-ortho xylidin 1 : 2.3..		223	134
a-ortho xylidin 1 : 2.4..	+49°	226	99
u-meta xylidin 1 : 3.2..		216	176.8
a-meta xylidin 1 : 3.4..		212	129
s-meta xylidin 1 : 3.5 ..		220	140.5
Para xylidin 1 : 4.2..		213.5	139

ACETANILID, $C_6H_5NHC_2H_3O$

The anilides are derivatives of anilin in which one or more of the hydrogen atoms of the amino group are replaced by acid radicles. The homologues yield similar derivatives and we therefore have toluides, xylidides, etc.

Unquestionably the most important derivative of anilin in the realm of pharmaceutical chemistry is acetanilid. This substance, which also goes by the name of phenylacetamide and antifebrin, is sold in enormous quantities as an antipyretic and analgesic and in various combinations with caffein, sodium bicarbonate, and bromides, occurs in by far the largest proportion of the headache mixtures sold on the market. Acetanilid is also used as an antirheumatic, anesthetic, and antiseptic, and for the latter purpose it will be found in hydrogen peroxide.

Acetanilid is usually dispensed in tablets or powders. The combinations include acetanilid with caffein and bromides, usually sodium; with caffein, bromides and sodium bicarbonate, sometimes with the addition of codein or heroin or quinin sulphate; with salol; with morphin; with quinin sulphate, with Gelsemium; with bromides, hyoscyamin and digitalin; with caffein and monobromated camphor; with salicylates, Gelsemium, monobromated camphor and hyoscyamin; with bromides, caffein, Hyoscyamus and morphin; with quinin, Hyoscyamus, arsenic, strychnin and Cannabis; with quinin, bromides, aloin, cascara, and Capsicum.

Acetanilid will also be found in liquids usually of the elixir type, where it is combined with bromides and caffein, to which are often added codein, Gelsemium, salicylates, antipyrin, and other drugs in combinations similar to those occurring in tablets.

Acetanilid is obtained by boiling a mixture of molecular proportions of anilin and glacial acetic acid under a reflux, and recrystallizing the resulting product out of water. It forms laminary crystals having a smooth feel, recalling that of boric acid, subliming at the temperature of the steam-bath, melting 111–113°, depending on the condition of its purity and distilling unchanged at 295°. It dissolves sparingly in cold water, but is fairly soluble in boiling water and readily dissolved by alcohol, ether, chloroform, or benzol. It is somewhat soluble in petroleum ether, and is removed from acid solutions by that solvent.

Acetanilid is a weak base and does not form stable salts with acids, nor give any precipitate with Mayer's reagent, iodin solution, nor picric acid. It is easily removed from an acid solution by immiscible solvents.

When warmed with potassium hydroxide and chloroform it yields phenyl isocyanide, thereby differing markedly from antipyrin and antiphenetidin, though the latter often gives a suggestive odor.

Its aqueous solution yields a precipitate with bromin water; this precipitate is a parabrom acetanilid, which is quite insoluble in water and melts 164–156° C. Acetphenetidin does not give any precipitate with bromin water. If this test is modified by digesting the acetanilid with dilute sulphuric acid 1 in 5, over the steam-bath for two or three hours and not allowing the hot acid to become concentrated enough to produce charring, the drug will be broken up into its basic substances, acetic acid evolved and anilin sulphate remaining in solution. The cold dilute solution will give a heavy flocculent precipitate with bromin water. Acetphenetidin under similar conditions yields phenetidin sulphate, and a blue color results on adding bromin water. This procedure allows for the simultaneous identification of both substances if they occur together.

If desired, the acid aqueous solution obtained by digesting the acetanilid may be treated with excess sodium hydroxide and liberated anilin shaken out with ether.

On boiling 0.1 gram of acetanilid for several minutes with 2 mils of hydrochloric acid and adding to the cool solution 3 mils of phenol 1 in 20 and a saturated solution of calcium hypochlorite, the mixture, which will be brownish red, will acquire a blue color with excess of ammonia water.

Acetanilid dissolves without change in concentrated sulphuric acid, and remains unchanged if heated at the temperature of the water-bath for half an hour. After exposure for four to five hours at this temperature,

it is converted mostly to sulphanilic acid with a small amount of acet-sulphanilic acid. Acetphenetidin when heated for an hour or two with concentrated sulphuric acid at the temperature of the water-bath yields phenetidin sulphonic acid. If a little water is present there is an evolution of ethyl acetate and para-amidophenol is formed which is subsequently changed to the sulphonate.

Watson [1] found that when acetanilid was mixed with boric acid in a porcelain dish and heated on a free flame an odor suggestive of sweet clover or arbutus was evolved and a yellow residue remained. Acetphenetidin left a yellow residue, but the odor was different and antipyrin gave a naphthalene odor and a pink residue. In the case of mixtures the odor was increased by adding a drop of water to the residue.

As acetanilid is removable from acid solutions by means of immiscible solvents it will appear in the general scheme of shake-out analysis in all the fractions obtained by shaking out the acid mixture. It will, of course, appear in greatest amounts in the ether and chloroform fractions, but small quantities are removed by petroleum ether. If the acetanilid is unaccompanied by any other substance removable from acid solution by immiscible solvents, its identification is easy, for it can be recrystallized from water and its melting-point and other characteristic properties determined. The carbylamine test should be first applied and if negative no further concern is necessary.

Caffein if present may be separated without difficulty by dissolving the residue in dilute hydrochloric acid and then throwing out the caffein with iodin. The acetanilid remains dissolved, and after the precipitation is complete, and filtration has been accomplished, it may be recovered from the filtrate by destroying the excess of iodin with sulphite, and then shaking out with chloroform. If it is desired to identify the caffein it is recovered from the iodin precipitate by solution in sulphite solution, and shaking out with chloroform from an ammoniacal mixture.

The presence of antipyrin is indicated by treating with Mayer's reagent a portion of an aqueous solution of a suspected mixture, obtained by shaking out an acid solution with immiscible solvent. If a well-defined precipitate is obtained with this reagent and subsequent tests with picric acid and nitric solution give the characteristic antipyrin reactions, a separation of the acetanilid may be effected by dissolving the residue in hot water allowing enough to hold up the acetanilid when cool, and precipitating the antipyrin with picric acid. On filtering the acetanilid can be recovered from the filtrate unchanged by shaking with chloroform and any picric acid carried along by the solvent is removable by shaking with dilute alkali. On evaporating the chloroform the acetanilid will be found in the residue and should be crystallized and examined for identification.

[1] Am. J. Pharm., 1911, 83, 269.

If it should happen that caffein were present simultaneously with the antipyrin and acetanilid, the same procedure for separating the antipyrin can be employed and the chloroform residue, containing the caffein and acetanilid, is treated exactly as described in the preceding paragraph. Antipyrin, and acetanilid in admixture cannot be satisfactorily separarated by crystallization, and when mixed the melting-point is depressed some 40–50°. In connection with a mixture containing antipyrin, the picrate ought to be separated, washed, and its melting-point determined, especially if the sample under investigation is to form the basis of litigation.

If the presence of acetanilid is indicated by the carbylamine reaction and caffein is absent, the presence of a phenetidin may be shown by treating the residue with dilute sulphuric acid 1 in 5, transferring to a small Erlenmeyer and heating over the water-bath for an hour or two, noting the odor evolved, and in cases of extreme importance collecting the vapors after running them through a condenser and testing them for acetic and formic acid. The acid solution in the flask is then diluted and treated with bromide-bromate reagent which will give a blue color if a phenetidin were present, and a simultaneous precipitate of anilin tribromide if acetanilid. It is doubtful if one will meet the three common antipyretics combined in one preparation and the employment of acetphenetidin and acetanilid together is rare, but in case one encounters a mixture where the preliminary tests with the residues indicates all of them a procedure along the following lines will enable the worker to draw the proper conclusion. The residue should be treated with dilute sulphuric acid 1 in 5 and heated on the steam-bath as described above, collecting the vapors and testing the distillate for formic, acetic, and other acids. The acid solution is then diluted with water and shaken out with chloroform, which will remove the antipyrin and caffein, and leave the phenetidin and anilin sulphates behind. The antipyrin and caffein can then be separated by picric acid and their identities established. The acid solution is then warmed to drive off any adhering chloroform, and on cooling is treated with iodin solution, which will precipitate the phenetidin in the form of an iodin compound. On filtering, the anilin is recovered from the filtrate by removing the excess of iodin with sulphite, adding excess of alkali and shaking out with ether.

The treatment of acetphenetidin with acid under the conditions above described affects only the radicle attached to the NH group. This fact should be borne in mind when drawing conclusions as to identity. If acetic acid is evolved and the residual solution gives the characteristic reactions, it is practically certain that acetphenetidin is present. If desired the residual solution can be acetylated with acetic anhydride and the original phenetidin reproduced.

For the evolution of methods for the determination of acetanilid in its various mixtures and the simultaneous determination of the accompanying ingredients we are indebted to W. O. Emery. His procedures are based on extended researches covering a period of many years, and the details have been perfected from the results of an elaborate system of cooperative work. The methods have appeared in the proceedings of the Association of Official Agricultural Chemists beginning in 1908 and they have been collected and published as a unit for the first time in this work. Acknowledgment and full credit is given him herewith.

SEPARATION OF CAFFEIN, ACETANILID AND SODIUM BICARBONATE

Caffein

Weigh out about 3 grams headache powder on a small (5.5-cm.) tared filter,[1] wash with successive portions of chloroform to the amount of about 30 mils, collecting the solvent in a 100-mil Erlenmeyer. Distill off chloroform by means of a small flame until only a few mils remain. Add 10 mils dilute sulphuric acid, and then continue the distillation till all the chloroform has gone over, disconnect from condenser, heat gently, first on wire gauze to complete solution,[2] finally on steam- or hot-water bath until contents of flask have evaporated to about 3 to 4 mils. Cool, transfer by washing with water to a separatory funnel so that the final volume does not greatly exceed 20 mils. Add four times the volume, or about 80 mils of chloroform, shake for some time vigorously, allow to stand until the chloroform clears perfectly, pass through a small dry filter into a dry 100-mil Erlenmeyer, distill off the solvent and use distillate for a second extraction, observing the same method of shaking, clearing and filtering as above noted. Distill off chloroform to a small volume, transfer residue to a small tared beaker or crystallizing dish by means of a few mils of chloroform. Allow to evaporate spontaneously or if desired on a steam- or hot-water-bath to dryness, in the latter case partially covering the dish toward end of operation with a watch-glass in order to avoid possible loss from "popping.' Cool in desiccator and weigh as caffein, dry alkaloid.[3]

[1] In cases of powder mixtures or tablets containing ground celery seed, much coloring matter, cinchona alkaloids, laxative or extractive principles other than acetanilid or phenacetin, it is our practice to shake out the latter from dilute sulphuric acid solution or suspension by means of chloroform.

[2] In case the preparation contains ground celery seed or certain oily principles it sometimes happens that the acid solution does not become entirely clear at this point.

[3] Should the caffein not be colorless or nearly so, the residue is dissolved in about 10 mils of water, filtered if necessary (in case oily matters are present) through a wet filter, and filtrate acidified with dilute hydrochloric acid, the caffein precipitated with

Acetanilid

First Method.—The acid solution remaining in separator and containing anilin sulphate is run into a 100-mil Erlenmeyer, the filter through which the chloroform passed is washed once with a little water, allowing latter to run into the separator. Rinse the latter thoroughly, adding the aqueous rinsings to acid solutions Now run in slowly and with constant agitation a standard solution of potassium bromide-bromate [1] to a faint but distinct yellow coloration. The number of mils employed, multiplied by the value of 1 mil in terms of acetanilid, will give the amount of acetanilid present.

Second Method.—The acid solution aforesaid is treated with successive small portions of sodium bicarbonate until an excess of this reagent is observed in the bottom of separator. Add 50 mils chloroform and 15 to 20 drops of acetic anhydride, shake for some time vigorously, allow chloroform to clear then pass through the same filter used for the caffein into a 100-mil Erlenmeyer, and distill off most of the chloroform. Use this distillate for a second shake out, clear, filter, and distill down to a small volume, transferring residue and subsequent chloroform washings to a tared beaker or dish precisely as in the case of caffein. Allow solvent to evaporate spontaneously or by means of a blast or fan, avoiding, however, undue heat.[2] Dry in desiccator over quicklime to constant weight.

Verify final weight by means of titration with standard potassium bromide-bromate solution as in the first method. Heat residue with 10 mils dilute sulphuric acid a half-hour on steam- or vapor-bath, cool, add 5 mils water and titrate as directed above.

Sodium Bicarbonate

The residue left after first treatment with chloroform is weighed when dry and represents very nearly the amount of sodium bicarbonate present. It may be more accurately estimated by titrating with N/10 sulphuric

15 to 20 mils of Wagner's reagent, allowed to stand a half hour, filtered and the precipitate washed with a few mils of same reagent, the filter together with precipitate transferred to separator, decolorized by means of sodium sulphite and the caffein finally extracted with chloroform.

[1] For this purpose the solution is prepared by adding bromin in slight excess to a concentrated aqueous solution of 50 mils caustic potash, the liquid diluted till the separated salts redissolve, boiled to expel any excess of bromin and finally made up to one liter. This solution is standardized with weighed amounts of acetanilid, or it may be so adjusted by further dilution so that 1 mil is exactly equivalent to 1 centigram. of acetanilid. For purposes of titration 1 to 2 decigrams are heated a half hour on the steam- or water-bath with 10 mils dilute sulphuric acid.

[2] Acetanilid suffers appreciable loss when heated above 40°.

acid, using congo red as indicator, or it may be ignited with dilute sulphuric acid and weighed as sodium sulphate.

Calculate results on parts per 100.

CAFFEIN, ANTIPYRIN, AND ACETANILID

A gross separation of these agents from other materials can usually be effected by a procedure similar to that applied to the more simple caffein-acetanilid mixtures. Owing to the very high solubility, however, of antipyrin in aqueous media, a complete extraction therefrom by means of chloroform involves a more protracted treatment with this solvent than is required in the case of caffein. The separation of both caffein and antipyrin from acetanilid is based upon the solubility of the former substances and the insolubility of anilin sulphate, into which the acetanilid must first be converted, in chloroform. Caffein and antipyrin are separated one from the other by virtue of their behavior toward mercuric nitrate, the antipyrin yielding under the conditions of the experiment a molecular compound with the mercury salt, practically insoluble in the medium in which the precipitation is effected. After filtration, chloroform extracts from an aliquot of the clear filtrate the caffein, which is weighed directly, while the antipyrin is estimated, after regeneration and recovery from its molecular combination with mercuric nitrate, by titration with standard alcoholic iodin.

Caffein

Dissolve an amount of antipyrin-caffein mixture containing not more than 1 gram of the former substance in a 200-mil glass-stoppered flask in about 150 mils saturated aqueous solution of potassium nitrate, heat on the steam-bath nearly to the boiling temperature, then treat, a few drops at a time, with a solution of mercuric nitrate (prepared by dissolving 25 parts red oxide of mercury in 60 parts of 25 per cent nitric acid by means of gentle heat, diluting with water to 200 mils then saturating this solution with potassium nitrate), the flask being agitated after each addition in order to clarify the liquid; 10 to 12 mils reagent should suffice to effect complete precipitation. Any undue excess of mercuric nitrate is to be avoided. On standing several hours or until the product has acquired the temperature of the room fill flask to mark with saturated solution of potassium nitrate, mix thoroughly, then filter by the aid of suction, using in this connection if available, a small (4-cm.) perforated plate and the requisite filter. Transfer an aliquot (100 mils) of the filtrate to a separatory funnel and extract five times with 50-mil portions of chloroform, the solvent from each extraction being run through a small pledget of

cotton and dry filter into a 200-mil Erlenmeyer. On completion of the third extraction, distill the chloroform down to about 40 mils, using the distillate thus obtained for the two final extractions. Add the chloroform from the fourth extraction to that remaining from the first three, transfer the whole to a second separator and shake vigorously with 5 mils water, in order to remove traces of potassium nitrate. Run the chloroform through cotton and filter into a second Erlenmeyer, to which is added the solvent, from the fifth or final extraction, after this has been subjected to washing in the second separator above mentioned. Distill the chloroform from the combined extractions down to a small volume, transfer residue to a small tared beaker, evaporate at the ordinary temperature or at a moderate heat on the vapor-bath, and weigh the residual caffein. If the various manipulations have been conscientiously carried out, it will be found that the product is very nearly pure. In any case it should be dissolved in water, a few drops of HCl added and the liquid saturated with H_2S. Should any quantity of the antipyrin-mercuric nitrate compound have been taken up by the chloroform, a faint coloration or even slight precipitate will result, which may be filtered off in a Gooch, dried and weighed. From the formula: $C_{11}H_{12}N_2O \cdot Hg(NO_3)_2$, it will be seen that 1 part of HgS would correspond to 2.21 parts of the molecular compound, hence the quantity of the latter, calculated from the amount of mercuric sulphide obtained, subtracted from the crude caffein would yield one-half the true amount of caffein present in the original mixture.

Antipyrin

The amount of this substance can be determined by difference provided the combined weight of both caffein and antipyrin is known, otherwise the estimation may be carried out as follows:

Weigh out on a small (5.5 cm.) filter an amount of the powdered sample equal to or a multiple of the average weight of one tablet, wash with successive small portions of 95 per cent alcohol, in quantity about 20 to 30 mils sufficient at least to extract all the antipyrin present in the mixture. Collect solvent in a 100-mil Erlenmeyer, add 10 mils of an alcoholic solution of mercuric chloride (5 grams in 100 mils 95 per cent alcohol), then run in a standard solution of pure iodin (1.351 grams resublimed iodin dissolved in 100 mils 95 per cent alcohol, 1 mil of which is either exactly or approximately equivalent to 10 mg. pure antipyrin until a faint yellow coloration persists. The number of mils required to bring about this result, multiplied by the value of 1-mil in terms of antipyrin will give the quantity of this substance present in the sample under examination.

Comments and Suggestions.—If desired the antipyrin can be readily recovered from its compound with mercuric nitrate. To this end collect

all the precipitate on the porous plate by the aid of saturated saltpeter solution, remove to beaker, add 50 mils water, acidify with HCl, then saturate first in the cold, finally in the heat with H_2S, filter and wash the HgS thoroughly with hot water, collecting filtrate in a porcelain evaporating dish. Neutralize the free acid with ammonia and evaporate on a steam-bath to about 10 mils. Transfer to a separatory funnel by the aid of water so that the final volume does not exceed 20 mils. Extract five times with 50-mil portions of chloroform, drying, and collecting the solvent in the usual way in an Erlenmeyer. Distill off most of the chloroform, transfer residue to a tared beaker by means of additional solvent, evaporate on a steam-bath to apparent dryness, cool, and weigh. Dissolve the antipyrin thus obtained in 95 per cent alcohol, and titrate all or an aliquot with standard alcoholic iodin.

ACETANILID AND QUININ SULPHATE

The separation of these two substances is based on the fact that the bisulphate of quinin in aqueous-acid solution is practically insoluble in U. S. P. chloroform, while acetanilid under the same conditions is readily taken up by this solvent. The procedure, therefore, resolves itself into the following steps:

Ascertain the weight of 20 or more tablets, reduce to a powder and transfer to a glass-stoppered or well-corked flask. Weigh out on a metal scoop, watch-glass, or other convenient object an amount of powdered sample equal to or a multiple of the average weight of one tablet, transfer to a separatory funnel (Squibb form), add 50 mils chloroform, 20 mils water and 10 drops dilute sulphuric acid, sufficient at least to insure a slight excess of this reagent in the mixture. Shake for some time vigorously, allow to clear, then draw off the solvent through a small pledget of cotton and a small (5.5 cm.) dry filter into a 200-mil Erlenmeyer. Repeat extraction twice, using the same amount of chloroform as in the first operation. Use a fresh pledget of cotton for each withdrawal of solvent, putting the moist cotton after passage of the chloroform into the filter, where with the latter it is allowed to dry spontaneously, or by placing a few moments on the cover of a steam-bath. On completion of the third extraction the separation of the two ingredients in question is practically complete, all the acetanilid being in the chloroform, while the quinin remains in the aqueous-acid solution, with traces also in both cotton and filter.

Acetanilid

Distill the chloroform from the three extractions by the aid of gentle heat down to about 10 mils, add 10 mils dilute sulphuric acid (1 : 10 by

volume), continuing the distillation until all the solvent has passed over. Remove to a steam- or vapor-bath and digest for about one hour or until the liquid has evaporated to about two-thirds the original volume. Add 20 mils water, digest thirty minutes longer, add 10 mils conc. HCl, then titrate with a standard solution of potassium-bromide-bromate, substantially as outlined in the method for the estimation of acetanilid and caffein.

Quinin Sulphate

Wash filter and cotton used in drying the chloroformic solution of acetanilid once with 5 mils water, allowing latter to run into the aqueous-acid solution of quinin. Add solid sodium bicarbonate (or aqueous ammonia) in slight excess, then extract with three 50-mil portions of chloroform, washing each portion in rotation with 5 mils water, and passing the solvent after clearing through cotton and a dry filter, exactly as in the extraction of acetanilid. Distill the chloroform from the several extractions down to about 10 mils then, if it seems desirable to weigh the quinin as such, transfer residue to a small tared beaker by pouring and subsequent washing with chloroform, evaporate to apparent dryness on the steam-bath, heat for an hour at 125° in an air-bath, cool, and weigh. If, as is usually the case in combinations like the one at present under examination, the weight of quinin sulphate is desired, distill the chloroformic solution of quinin to apparent dryness by means of gentle heat, dissolve residue in 3 to 5 mils neutral alcohol (just sufficient to prevent precipitation by the standard acid) and titrate with N/50 sulphuric acid (using two drops methyl-red solution as indicator) till color changes to faint red. Remove to steam-bath and heat until most of the alcohol has been expelled, the color of the liquid having in the meantime become yellow again. Now add sufficient acid to restore the faint red coloration, note number of mils expended, then multiply same by 8.66 the value of 1 mil N/50 sulphuric acid in mgs. of quinin sulphate $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 7H_2O$, to get the weight of this substance in sample taken. In the event that the quinin as such has first been weighed, the weight should be further checked by titration, substantially as outlined above.

Comments and Suggestions.—The composition of many medicinal preparations in pill or tablet form is frequently of such a nature as to completely inhibit any rational separation of the active organic constituents by means of immiscible solvents in the ordinary separatory funnel, owing to the formation of persistent emulsions even on cautious agitation. To obviate this difficulty various flattened types of separators have been suggested one of which illustrated on page 25, yields gratifying results, a twenty-minute treatment on the rotating table suffices to effect a maximum distribution of the substances involved. Wherever available such

separators will be found highly advantageous in obviating the delay and annoyance occasioned by emulsifying mixtures.

Since quinin sulphate readily loses a portion of its water of crystallization when exposed to dry air, the amount of sulphate found, whether calculated from quinin as weighed or from that determined volumetrically, need not necessarily correspond with the declared amount of this commodity indicated on the sample under investigation.

ACETANILID, QUININ SULPHATE AND MORPHIN SULPHATE

As in a mixture of acetanilid and quinin sulphate, so likewise in the present combination, the alkaloidal constituents in aqueous-acid solution are separated from the third by virture of the insolubility of their sulphates in chloroform. The separation of the alkaloids themselves is based on the ability of morphin to yield with an alkaline base a morphinate insoluble in chloroform. The procedure thus resolves itself into the following particulars.

Acetanilid

Transfer to a separatory funnel an amount of the powdered sample equal to or a multiple of the average weight of one tablet (the amount of morphin sulphate represented should not be less than $\frac{1}{4}$ grain), add 20 mils water and 10 drops dilute sulphuric acid, then extract with three 50-mil portions alcohol-free chloroform, the subsequent manipulations being substantially as directed for this ingredient in the combination: Acetanilid and Quinin Sulphate.

Quinin Sulphate

Wash filter and cotton used in drying the chloroformic solution of acetanilid once with 5 mils water, uniting latter with the aqueous-acid solution and quinin and morphin. To this solution add 4 to 5 mils aqueous sodium hydroxide (5 grams pure NaOH in 50 mils water), then extract with three 50-mil and one 25-mil portions U. S. P. chloroform, transferring latter in rotation to a second separator (Squibb type) containing 5 mils water, wash, and pass the nearly clear chloroform through a pledget of cotton and small filter into a 200-mil Erlenmeyer, from which the solvent is later removed by gentle distillation and the residue titrated, substantially as outlined for quinin in the combination: Acetanilid and Quinin Sulphate.

Morphin Sulphate

Wash filter and cotton employed in the preceding operation with 5 mils water, which latter together with that portion used to wash the

chloroformic solution of quinin is united with the aqueous-alkaline solution of sodium morphinate. Now add 0.5 gram ammonium chloride (an amount slightly in excess of that required to free the morphin as well as convert the NaOH into NaCl) and to the resulting ammoniacal solution, add 45 mils U. S. P. chloroform and 5 mils alcohol, then extract and draw off solvent into a second separator containing 5 mils water, wash, allow to clear, then pass chloroform through cotton and filter into a 200-mil Erlenmeyer. Repeat extraction and subsequent washing with one 50-mil, one 40-mil, and one 30-mil, U. S. P. chloroform, finally collecting the solvent from all extractions and distilling from the aforesaid Erlenmeyer down to about 10 mils. Transfer by pouring and washing with additional chloroform to a small tared beaker, evaporate on the steam-bath to dryness, cool, and weigh the residual morphin now appearing as a transparent varnish. To render crystalline, dissolve by warming with 1 mil neutral alcohol, add about the same quantity of water drop by drop, rubbing the glass with a rod to induce crystallization, then evaporate slowly on the steam-bath to dryness. Cool and weigh a second time. Check the weight of morphin thus found by titration with N/50 sulphuric acid, using a drop of methyl-red solution as indicator. To this end dissolve the morphin in 1 to 2 mils warm neutral alcohol, then after solution is complete add the acid till color changes to faint red. Evaporate most of the alcohol on the steam-bath, and in the event that the color has reverted to yellow add just sufficient acid to restore the faint red coloration. Note volume of acid expended, then multiply the number of mils by 7.53 (the number of mg. morphin sulphate equivalent to 1 mil N/50 sulphuric acid) to ascertain the quantity of morphin sulphate in the sample taken. The amount of anhydrous or of crystallized alkaloid can also be determined from the titration value by use of the proper factor.

Comments and Suggestions.—For the purpose in question alcohol-free chloroform may be conveniently prepared by washing the pharmacopeal product several times with water.

All cotton used for drying chloroform should first be freed from fatty material or other extractives by thorough washing with this solvent, all of which latter may be regained by distillation.

In the various operations involving fixation and subsequent liberation of morphin by means of fixed alkali and ammonium chloride, strict attention should be paid to the matter of adding these reagents, since any undue excess of either might nullify the entire procedure. Any large excess of NaOH would naturally require for its reduction a correspondingly large amount of NH_4Cl, the latter in turn yielding its pro rata of NH_4OH, relative large quantities of which through interaction with NaCl tend to inhibit any permanent liberation of the alkaloid and thus prevent a complete extraction. Furthermore, the presence of relatively large quan-

tities of NH_4OH as such operates to a partial retention of morphin in solution, due in part, possibly, to the formation of the hydrochloride of this alkaloid.

In spite of all precautions in the matter of excluding impurities from morphin, the amount of this substance as found by weight will usually be greater than that determined volumetrically. In order to insure greater accuracy in volumetric operations with alkaloidal substances as quinin, morphin, etc., the suggestion is made, in all cases where possible, that the strength of the standard acid used be checked by titration against the pure alkaloid under examination.

ANALYSIS OF MIXTURES CONTAINING CODEIN, ACETANILID, AND SODIUM SALICYLATE

The separation and estimation of these three substances is effected in the following manner: Reduce 20 tablets to a fine powder, then weigh out an amount equal to the average weight of one tablet, transfer to a separatory funnel, add 50 mils chloroform, 10 mils of water, and about 1 mil of dilute sulphuric acid, sufficient to insure acidity in the solution. Shake vigorously, allow to clear, then draw off solvent through a pledget of cotton and dry filter into a second separatory funnel of about 200 to 250-mil capacity. Extract a second and third time, using the same amount of chloroform as before. After each withdrawal of the solvent throw the cotton pledget into the separator and substitute a fresh one in its place. Treat the combined chloroformic extracts as directed under acetanilid.

Codein

Wash the filter used to dry the chloroform solution of acetanilid and salicylic acid with 5 mils of water, receiving latter in the separator containing the aqueous acid solution of codein. Add solid sodium bicarbonate in slight excess, then extract by means of vigorous shaking with three 50-mil portions of chloroform. Dry the solvent with cotton and filter as above, collect in 200-mil Erlenmeyer, then distill the liquid by the aid of gentle heat down to about 10 mils. Transfer the residue by pouring and rinsing with fresh chloroform, to a small tared beaker, evaporate to apparent dryness on the steam-bath, cool, and weigh as anhydrous codein. Verify by moistening the residue with a little neutral alcohol and titrating with N/50 sulphuric acid, using methyl red (1 drop alcohol soluble) as indicator.

Acetanilid

To the chloroform solution of acetanilid and salicylic acid add 20 mils of water, and for every 100 mg. of salicylic acid known or believed to

be present, 1 gram of anhydrous sodium carbonate. Shake vigorously, allow to clear, withdraw the chloroform through cotton, and filter into a 200-mil Erlenmeyer. Extract the aqueous-alkaline solution with two 10-mil portions of chloroform in order to remove traces of acetanilid taken up temporarily by the water. Distill the united chloroformic extracts by the aid of gentle heat down to about 10 mils. Introduce into flask 10 mils of dilute sulphuric acid (1 : 10 by volume) and digest on the steam-bath until the residue amounts to 3 to 5 mils then add 20 mils of water and 10 mils of concentrated hydrochloric acid. Into this solution run slowly a standard solution of potassium bromide-bromate until a distinct yellow coloration persists. Multiply the number of mils required to complete the formation of tribromanilin by the value of 1 mil in terms of acetanilid to ascertain the amount of this substance originally present in the sample taken.

Sodium Salicylate

Transfer the aqueous soda solution containing the salicylic acid from the separator to a 200-mil Erlenmeyer, dilute with water to about 100 mils, heat nearly to boiling, then run in from a burette 25 to 50 mils of N/5 iodin in potassium iodide (or double this quantity of N/10 strength) sufficient to insure an excess of this reagent. Digest the product on the steam-bath for one hour, adding iodin solution from time to time in order to maintain a slight excess. The reddish, insoluble precipitate has the composition $(C_6H_2I_2O)_2$, being identical with the " red substance " first described by Lautemahn [1] and later used by Bougault [2] in the separation of salicylic from benzoic and cinnamic acids. Remove any excess of iodin by the addition of a few drops of sodium thiosulphate solution, decant liquid through a tared Gooch, care being taken that most of the precipitate remains in the flask. Add 50 mils of boiling water to the latter, digest ten minutes on steam-bath, then pour into Gooch, into which all the reddish precipitate is gradually washed, using for this purpose and subsequent washings about 200 mils of hot water. Dry in air-bath to constant weight. The weight of precipitate multiplied by 0.4658 will give the amount of sodium salicylate originally present in the sample.

Should acetphenetidin instead of acetanilid be employed in the above combination, the procedure need be modified only to this extent, that the chloroform solution of acetphenetidin and salicylic acid, after elimination of the latter substance through treatment with sodium carbonate, is distilled down to about 10 mils and the residue transferred to a small crys-

[1] Liebig's Annalen, 1861, 120: 309.
[2] J. Pharm. Chim., 1908, 28, 145.

tallizing dish for final evaporation of solvent and weight of resulting acetphenetidin.

In this connection it may not be amiss to state that the quantitative separation of codein, acetanilid, and sodium salicylate could be effected in substantially the following manner: To the mixture in separatory funnel add about 100 mg. of sodium bicarbonate, 10 mils of water and 50 mils of chloroform. Extract three times with this quantity of solvent. The sodium salicylate remaining in the separator is transferred to an Erlenmeyer and treated with iodin solution as above directed, after the extraction of codein and acetanilid is accomplished by shaking out the chloroform solution of these two substances with 10 mils of dilute sulphuric acid. The acid solution is washed twice thoroughly with about 10 mils of chloroform in order to remove traces of acetanilid taken up temporarily by the aqueous medium. The latter substance, after removal of solvent and subsequent hydrolysis, is titrated with standard bromide-bromate solution, as already described. The aqueous-acid solution of codein is treated with solid sodium bicarbonate in excess, the alkaloid thereupon extracted with chloroform. On removal of solvent by distillation and evaporation the codein is first weighed and then titrated with N/50 sulphuric acid.

ESTIMATION OF CAFFEIN, ACETANILID, QUININ, AND MORPHIN

Weigh out an amount of the powdered sample containing at least one-fifth grain (about 12 mg.) of morphin, transfer to a separatory funnel, adding 20 mils of water, 10 drops of dilute sulphuric acid, and 60 mils of alcohol-free chloroform. Shake vigorously, allow to clear, then draw off through a pledget of cotton and small dry filter into a second separator, in which the solvent is washed with 5 mils water to remove any alkaloidal traces that may have been taken up by the chloroform. The latter is finally passed through a small filter into a 200-mil Erlenmeyer for subsequent distillation and treatment in the separation of caffein and acetanilid.

Quinin

Repeat the extraction of the aqueous-acid mixture with 50, 40, and 30-mil portions of chloroform, each portion of solvent being treated as directed for the first. The wash water is returned to the first separator, the liquid rendered alkaline by the addition of strong caustic soda in slight excess. We now have the morphin as sodium morphinate insoluble in chloroform, while the quinin is precipitated as a white flocculent mass. Shake out four times with 60-, 50-, 40- and 30-mil portions of alcohol-free chloroform, the solvent from each operation being passed through

cotton and a dry filter, prior to reception in the Erlenmeyer and distillation from the quinin dissolved therein. Transfer to a small tared beaker by pouring and rinsing with a small quantity of chloroform, evaporate to apparent dryness on the steam-bath, heat amorphous residue one hour at 125° C. in an air-bath, cool, and weigh. Dissolve in alcohol, transfer to a graduated 100-mil flask, fill to mark with water and sufficient alcohol to prevent precipitation of alkaloid; then remove with a pipette an aliquot containing at least one-tenth of the total amount of quinin present and titrate with N/50 sulphuric acid, using as indicator 1 to 2 drops of methyl red (100 mg. dissolved in 100 mils of alcohol). The number of mils required multiplied by 8.66 will give the number of milligrams of quinin sulphate in the aliquot titrated.

Morphin

In order to recover the morphin from its combination with sodium, add an amount of ammonium chloride slightly in excess of that required to react with the caustic soda previously introduced into the separator and as much common salt as the liquid will dissolve. A slight excess of the latter substance above that necessary to saturate the mixture can do no particular harm other than render the subsequent removal of the chloroform less quantitative. Extract four times by means of vigorous shaking with 50-, 45-, 40-, and 30-mil portions of Pharmacopœial chloroform, to the first portion of which are added 5 mils of alcohol prior to extraction. Wash each portion of solvent in a second separator with about 5 mils of water, after extraction but before passing through cotton and filter into a 200-mil Erlenmeyer for distillation. Distill off most of the solvent, transfer residue by pouring and rinsing with fresh chloroform to a tared crystallizing dish, evaporate to apparent dryness on the steam-bath, treat residue with a few drops dilute alcohol should it seem desirable to obtain the morphin in crystalline form, heat again to dryness, cool and weigh. Verify by dissolving the alkaloid in a few mils of warm alcohol and titrating with N/50 sulphuric acid, using as indicator a drop of methyl red solution. The number of mils required multiplied by 7.53 will give the number of milligrams of morphin sulphate present in the original sample.

Caffein

Distill the chloroformic solution of caffein and acetanilid down to about 10 mils, add 10 mils of dilute sulphuric acid (1 : 10), digest on steam-bath until contents of flask have evaporated to about 5 mils, add 10 mils of water and evaporate a second time; transfer residue to a separator by pouring and rinsing with water so that the final volume does not exceed 20 mils, then make three extractions with 50-mil portions of chloroform.

After clearing, pass solvent through cotton and dry filter into a 200-mil Erlenmeyer; distill from the combined extractions down to about 10 mils then transfer to a small tared crystallizing dish by pouring and careful rinsing with small quantities of fresh chloroform. Allow to evaporate spontaneously, or at a moderate heat, on a vapor-bath to apparent dryness. Remove from heat immediately on the appearance of a crystalline residue. Cool in a desiccator and weigh as anhydrous caffein.

Acetanilid

Draw off the acid solution remaining in separator into the same Erlenmeyer previously used in effecting the hydrolysis, wash out separator several times with water to insure complete removal of former contents; heat the aqueous-acid solution a short time on steam-bath to expel all traces of chloroform; wash the filter used in the preceding operation to dry the chloroform solution of caffein at once with 5 mils of water, receiving latter in the main solution of anilin sulphate; add 10 mils of concentrated hydrochloric acid, and titrate with a standard potassium bromide-bromate, 1 mil of which is equivalent to 10 mg. of pure acetanilid. The number of mils required to complete the precipitation, multiplied by the value of 1 mil in terms of acetanilid, will give the quantity of this substance originally present in the sample taken. In the event that the quantity of acetanilid present in the tablet is relatively large, as is frequently the case when compared with the morphin content, it is best to titrate only an aliquot of the anilin sulphate solution.

METHOD FOR ANALYZING LIQUID HEADACHE MIXTURES. EMERY[1]

Alcohol

Cool sample to 25° C., at which temperature fill a 25-mil flask to mark, weigh, then transfer to a distilling apparatus, rinsing out the flask several times with water, employing for this purpose a total of 25 mils. Distill into a 50-mil flask (surrounded by ice-water) until the liquid in the distilling flask is reduced to 10 mils. Transfer the somewhat turbid distillate (due to volatile oil) to a separator provided with short delivery tube, rinse out the flask several times with a total of 15 mils water, saturate the combined solution with sodium chloride, shake vigorously for two minutes with 25 mils low boiling (40–60° C.) petroleum ether, then allow to stand fifteen minutes. Draw off entire liquid into a second separator, washing out the first (which still contains undissolved salt) with 5 mils saturated salt solution into the second. Draw off the lower layer into first separator, from which the undissolved salt has in the meantime been

[1] U. S. Dept. Agri. Bu. Chem. Bull., 152, p. 256.

removed, and shake it out as above with a second portion of 25 mils saturated solution, transferring resultant mixture to the distillation flask. Distill into a 50-mil flask (cooled in ice-water) nearly to mark, allow temperature to rise to 25° C., fill to mark, and determine the specific gravity at this temperature in a Squibb pyknometer, calculating the per cent of alcohol by volume from tables. The percentage obtained multiplied by 2 will give the amount of alcohol in original sample.

Caffein-Acetanilid

Transfer residual crystalline magma containing the caffein, acetanilid, and sodium salicylate from distilling flask to a separatory funnel by the aid of successive portions of water (ending with a little chloroform if necessary to remove all traces of acetanilid) so that the final volume of the aqueous solution does not exceed 50 mils. Make five separate extractions by means of vigorous shaking, each time with 70 mils chloroform. Allow solvent to clear after each extraction, pass through small (5.5-cm.) dry filter into a 200-mil Erlenmeyer and distill by the aid of a small flame until about 60 mils have gone over. Use this distillate for each subsequent extraction, making up to 70 mils as found necessary with fresh solvent. After the final extraction and distillation of chloroform, add 10 mils dilute sulphuric acid and evaporate to 4 or 5 mils on steam-bath, transfer the residual acid solution of caffein and anilin sulphate to a 100-mil graduated flask, fill to mark and determine caffein and acetanilid in an aliquot of 25 mils as directed in method for Estimation of Caffein, Acetanilid, and Sodium Bicarbonate.

Sodium Salicylate (Salicylic Acid)

The aqueous solution remaining in separatory funnel and containing the sodium salicylate and glycerin is rendered acid with hydrochloric acid and extracted three separate times by means of vigorous shaking, 70 mils chloroform being employed for each extraction. The solvent, after clearing, is run into a 200-mil Erlenmeyer (containing 10 mils water and 1 gram dry sodium carbonate, sufficient to fix all the salicylic acid present) and distilled over a small flame until most of the chloroform has been expelled. After the final distillation and elimination of all chloroform, transfer the aqueous soda solution of sodium salicylate to a liter flask, add 10 grams dry sodium carbonate, fill to mark, pipette an aliquot of 100 mils into a 200-mil Erlenmeyer, heat nearly to boiling, then add about 35 mils N/5 iodin in potassium iodide (or double this quantity of N/10 iodin solution), enough to ensure an excess of iodin. Heat one hour on steam-bath to near the boiling temperature, during which time a violet-red precipitate of tetraiodophenylenquinon, $(C_6H_2I_2O)_2$, will

appear. Remove excess of iodin by the addition of a few drops of hypo solution, decant liquid off into a tared Gooch crucible, care being taken that most of the precipitate remains in the flask. Add 50 mils boiling water to the iodin compound in flask, digest for ten minutes on steam-bath, then pour into the Gooch, into which the precipitate is gradually washed by means of hot water, using for this purpose about 200 mils. Dry to constant weight in air-bath at 100° C. Multiply weight of precipitate by 0.4658 and the product will be the weight of sodium salicylate in aliquot taken. Report all results in parts per 100.

Methyl Acetanilid—Exalgin, $C_6H_5N(CH_3)C_2H_3O$

Methyl acetanilid crystallizes in needles or tablets, melting 100–101° C. It is soluble in alcohol and boiling water, but only slightly in cold water. When hydrolyzed with acid it gives acetic acid and methyl anilin. The latter substance resembles anilin, but is lighter than water and boils 192°, and a solution of calcium hypochlorite colors it violet and then brown.

Acetanilid, and exalgin may be distinguished by the following reaction: about 0.05 gram is treated with 10 drops of hydrochloric acid and boiled for two minutes. The liquid is then cooled, 5 more drops of hydrochloric acid are added, then 1 drop of 1 per cent sodium nitrite solution; after allowing reaction to take place for ten minutes, 1 mil of phenol is added and then gradually enough strong sulphuric acid to give a homogeneous mixture. Of this 0.5 mil is treated with sufficient caustic soda solution; sp. gr. 1.332, to give a clear solution. In the case of exalgin a blue color will be obtained and with acetanilid a yellow tint. Mixtures will naturally vary from yellowish to green. The various details of the test must be rigorously observed.

It is used medicinally as an analgesic and antirheumatic.

Ethylacetanilid, $C_6H_5N(C_2H_5)C_2H_3O$

Ethylacetanilid melts 50° C.

Iodacetanilid

Acetparaiodanilid, $C_6H_5NHI(C_2H_3O)$. Iodacetanilid melts 181–182° C., soluble in alcohol and glacial acetic acid, insoluble in water.

Salifebrin

Salifebrin or " salicylanilid " is the name given to the product obtained by the fusion of salicylic acid and acetanilid.

Formanilid, $C_6H_5NH(HCO)$

Prepared from anilin and formic acid similarly to formation of acetanilid. It forms colorless crystals, melting 46°, soluble in alcohol, water, and glycerin. Its physiological properties are similar to acetanilid, and it has many similar chemical properties as would be expected from its similarity in composition. On heating with dilute sulphuric acid, formic instead of acetic acid is disengaged, thus furnishing important evidence as to its identification.

Gallanilid, Gallanol, $C_6H_5NHCOC_6H_2(OH)_3+2\,H_2O$

Gallanol is the anilid of gallic acid. It is a brownish crystalline substance, melting 205° C., soluble in alcohol, ether, and boiling water, and insoluble in chloroform. It is used as an antiseptic in skin diseases. It combines the properties of an anilid and gallic acid and on hydrolysis may be split up into its components which are then separable and can be identified.

Benzanilid, Phenylbenzamide, $C_6H_5NH(COC_6H_5)$

Benzanilid is a white or reddish-white crystalline substance, melting 160–162° C., soluble in alcohol, somewhat in ether but only slightly in water. It is used as an antipyretic.

Acettoluides

The toluides have already been mentioned on page 833. These bodies have some value as antipyretics and may be substituted for acetanilid in headache mixtures. Their general properties will of course simulate those of acetanilid, but they will yield toluidines on hydrolysis with acids. The ortho and meta compounds have a melting-point which is in close proximity to that of acetanilid.

Pyoktanins

Rosaniline base is triamidotolyl diphenyl carbinol.

$$NH_2C_6H_4C(OH)\begin{cases} C_6H_3(CH_3)NH_2 \\ C_6H_4NH_2 \end{cases}$$

Dyes of this type may be considered as derivatives of triphenyl methane. In pararosaniline the amido tolyl group is replaced by the amido phenyl. By use of various homologues of anilin many other compounds are possible and have been prepared.

Pyoktanin Blue

This compound consists of the hydrochlorides of penta and hexamethylpararosaniline and is a violet powder. It is soluble in alcohol, chloroform, water, and glycerin and insoluble in ether. It is a valuable antiseptic and disinfectant and is used in diseases of the mucous membrane and especially in veterinary practice, for it has been found to be a valuable remedy in the foot and mouth disease. It is dispensed in solution in capsules and in pencils, and is sometimes applied combined with mercuric chloride.

Pyoktanin Yellow

Pyoktanin yellow or auramine is imino-tetramethyl diaminodiphenylmethane hydrochloride. It is a yellow powder somewhat resembling sulphur and is soluble in alcohol and water. It is employed in skin diseases and in ophthalmic practice.

AMINOPHENOLS AND THEIR DERIVATIVES

Phenetidins

When carbolic acid is added to nitric acid sp. gr. 1.11 in the cold a mixture of ortho and para nitrophenols is formed. The former may be separated by steam distillation, and the latter which is left behind, dissolves in hot water from which it separates on cooling. The meta body is prepared by reducing meta-dinitrobenzol, diazotizing with dilute sulphuric and nitrous acid and then boiling, by which process the meta nitrophenol is produced.

On reduction, corresponding amino compounds are obtained. The acid character of the phenol is lost in presence of the amino group and the products yield salts only with acids, but they may still be esterified on the hydroxyl and the hydrogen of the amino group is replaceable by radicles.

These esterified bodies are called anisidins or phenetidins, according to the radicles present, the methoxy group gives the former, and the ethoxy the latter. Then, of course there are the *o*-, *m*-, and *p*-modifications of each.

The acetylated phenetidins are the substances of this group which have received the greatest attention by the medical profession and the manufacturing pharmacist. The best known is acetphenetidin or phenacetin. In preparing them the general procedure consists in esterifying the hydroxyl group of the nitro phenol before reducing the nitro group, and after accomplishing the reduction and separating, the acid radicle is introduced into the amino group.

A tabulation of the aminophenols and their principal derivatives follows:

	Ortho		Meta		Para	
	M.pt.	B.pt.	M.pt.	B.pt.	M.pt.	B.pt.
Aminophenol, $C_6H_4\langle^{OH}_{NH_2}$	170°	Sub-limes			184°	
Acetyl deriv., $C_6H_4\langle^{OH}_{NHCOCH_3}$	201°				179°	
Methyl Ester, (Anisidin)		228°		251°	56°	246°
Ethyl Ester, (Phenetidin)	242°	229°		180–205° at 100 mm.		253°
Methacetin, $C_6H_4\langle^{OCH_3}_{NHCOCH_3}$	84°	204°			127°	
Acetphenetidin, $C_6H_4\langle^{OC_2H_5}_{NHCOCH_3}$	70°			96–70°		135°
Phenocoll, $C_6H_4\langle^{OC_2H_5}_{NHCOCH_2\,NH_2}$						100.5°

Para-acetanisidin, Methacetin, $C_6H_4\langle^{OCH_3}_{NHCOCH_3}$

This a crystalline substance, melting 127°, slightly soluble in cold water, ether, and petroleum ether, but dissolves without difficulty in boiling water, alcohol, acetone, chloroform, dilute acids, and alkalies. When boiled with insufficient water to effect its complete solution, the undissolved portion melts, resembling acetanilid in this phenomenon, but differing entirely from acetphenetidin. It is used for the same purposes as its homologue.

Para-acetphenetidin

Para-acetphenetidin or phenacetin is the most important substance in this group. It is used for the same purposes as is acetanilid and in general may be stated to occur in mixtures of the same ingredients.

It is a white crystalline substance, melting 134-136° C., very slightly soluble in cold water, and somewhat more in boiling, and readily in alcohol, chloroform, and ether. It is removable from an acid mixture slightly by petroleum ether and quite completely by ether. Cold dilute sulphuric acid does not dissolve it, but on digesting for an hour with acid of 1 to 5 strength it goes into solution with evolution of acetic acid and formation of phenetidin sulphate. This acid solution on dilution gives a blue color with bromin water, but no precipitate, and it also gives a beautiful greenish-black iridescent precipitate with insufficient iodin solution to effect a complete conversion, but on adding excess the crystals change to an oily deep brownish-red resin. Acetphenetidin itself in aqueous solution does not give any precipitate with iodin, neither is it precipitated by Mayer's reagent nor bromin water.

If 0.1 gram of acetphenetidin is boiled for one minute with 1 mil concentrated hydrochloric acid, the solution diluted with 10 mils water, and filtered, a ruby-red color should appear on adding 3 drops chromic acid (1–30). The anilides do not react in this way.

It does not yield anilin on boiling with alkalies, but when warmed with alkali and chloroform there may develop a slight suggestion of isonitrile after several minutes. A solution resulting from boiling with alkali is not colored by the addition of sodium nitrite and dilute nitric acid and again boiled, but the solution obtained with acids gives a yellow precipitate with mercurous nitrate, which does not dissolve on boiling.

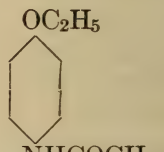
Unconverted paraphenetidin may be detected in para-acetphenetidin by adding about .5 gram of the sample to 2.5 grams chloral hydrate, which has been heated to 100° C., when a rich violet to purple-violet color appears if the impurity is present. Acetphenetidin alone gives a pinkish tinge after several minutes. It may also be detected by shaking the sample with hot water, cooling, filtering, acidifying with dilute sulphuric acid, and adding a drop or two of iodin solution which will cause a precipitate in presence of phenetidin, but not with acetphenetidin.

The presence of acetanilid in acetphenetidin is so readily detected that its use as an adulterant is now almost precluded. Acetphenetidin gives but a faint isonitrile reaction and this only on standing some minutes, while acetanilid gives it at once, and the presence of but a trace can be detected by this alone. Acetphenetidin does not give the reaction with phenol and bleaching powder which is characteristic of the anilides; on boiling with alkali there is no separation of anilin and on hydrolysis with dilute sulphuric acid and the resultant acid solution diluted, there is no precipitate given by bromin water. Hence, if a sample is suspected of being adulterated the application of the above tests will be sufficient to establish the actual conditions.

The question as to whether acetphenetidin is an acetanilid derivative

is still open legally. When the Food and Drugs Act was written acetanilid was included in the list of inhibited drugs and the regulations for its enforcement enumerated acetphenetidin among its derivatives. One of the Attorney Generals, at the request of the Department of Agriculture, wrote an opinion, based on information submitted by the Bureau of Chemistry, in which the position was taken that a derivative need not be a substance actually derivable or preparable from another substance by chemical means, but may be such by chemical relationship or substitution. On the other hand, the manufacturers take the position that acetphenetidin cannot be obtained from acetanilid, and therefore it should not be classified as its derivative. Looking at the space relationship of the two it is apparent that acetphenetidin might be called paraethoxyacetanilid.

Acetanilid



Acetphenetidin

As a matter of fact, however, acetphenetidin cannot be obtained directly from acetanilid by chemical means; by that is meant the introduction of the ethoxy group in the paraposition of the acetanilid molecule. It is, of course practicable to carry out the following train: acetanilid → anilin → phenol → nitrophenol → ethyoxy nitrophenol → phenetidin → acetphenetidin. But this is one of the possibilities of synthetic chemistry, and is applicable to thousands of other substances. Synthetic chemistry has advanced to such a state that it is possible to work forward and backward through numberless compounds, to pass from the aliphatic to the aromatic series, and starting with sufficient quantity of a given substance to eventually arrive at countless others. Antipyrin, salicylic acid, oil of wintergreen, acetylsalicylic acid (aspirin), and many other well-known drugs are just as much derivatives of acetanilid as is acetphenetidin if the argument is valid that by any hook or crook you can obtain one substance from another and call it a derivative of the original.

Both the ortho and meta acetphenetidin are known and resemble each other closely in their physical properties. The meta is unimportant.

The ortho and para bodies may be differentiated by the wide variance in their melting-points and the difference in the boiling-points of the phenetidins which result on boiling with dilute hydrochloric acid and which may be separated from the acid liquid by rendering it alkaline and shaking out with ether or chloroform. The para compound is completely changed to acetic acid and *p*-phenetidin sulphate when digested for an hour with sul-

phuric acid 1 in 5, but the ortho compound requires the action of stronger acid sp. gr. 1.575 for two hours at 90°. If in either case this resulting acid solution be diazotized, and then treated with an ammoniacal solution of naphthol-disulphonic acid, a fine reddish-yellow color appears in the case of the para body, and a cherry-red if the ortho is present.

The best methods thus far evolved for the quantitative assay of acetphenetidin mixtures are the result of the researches of Dr. W. O. Emery and his associates.

METHOD OF ANALYSIS OF MIXTURES CONTAINING CAFFEIN, ACETPHENETIDIN, ETC.

Determine the weight of 20 tablets, powder finely, and weigh out on a small (5.5 cm.) tared filter an amount equal to the average weight of 1 tablet. Wash with successive small portions of chloroform to the amount of 40 to 50 mils sufficient at least to insure complete extraction of all caffein and acetphenetidin in the mixture, collecting solvent in a 200-mil Erlenmeyer. Distill off chloroform by means of a small flame until only a few mils of solvent remain in the flask, using if possible in connection with this and similar operations a small spray trap. Add to the residual liquid 10 mils of dilute sulphuric acid (1 volume concentrated acid to 10 of water) and digest on a steam- or vapor-bath until contents of flask have evaporated to about 5 mils, then add 10 mils of water and continue digestion until the residue again amounts to about 5 mils. The quantitative separation of caffein from acetphenetidin depending, as it does, on a complete hydrolysis of the latter into acetic acid and phenetidin, every effort should be exerted to the end that all particles of acetphenetidin which may appear on the sides of the flask be gradually made to disappear in the acid liquid by a gentle rotation of flask during the process of digestion or by the addition of a few drops of alcohol or chloroform.

Caffein

Cool, pour, and rinse with water into a separatory funnel, so that the final volume does not greatly exceed 20 mils. Extract three times by means of vigorous shaking with thrice the volume of chloroform, in the present instance 60 mils. After clearing, pass through a small pledget of cotton (thrust up into the delivery tube of separator) and a small (5.5 cm.) filter into a 200-mil Erlenmeyer, being careful to recover any caffein which may cling to the apex of the delivery tube and edge of filter by washing with a little fresh chloroform. The pledget of cotton is removed by means of a wire and thrown into the separator on the completion of each extraction, a fresh one being introduced into the delivery tube prior to each subsequent withdrawal of solvent. Distill the chloro-

form from the combined extractions until the liquid is reduced to about 10 mils then transfer to a small tared beaker or crystallizing dish by pouring and careful rinsing with small quantities of chloroform. Allow to evaporate spontaneously or at a moderate heat on a vapor bath to apparent dryness, partially covering the dish with a watch-glass toward the end of the operation in order to avoid possible loss by decrepitation. Remove dish from heat immediately on the appearance of a crystalline residue. Cool in desiccator and weigh as anhydrous caffein. If caffein residue is impure due to fats, essential oils, coloring matter, etc., purify as directed under caffein-acetanilid mixtures.

Acetphenetidin

Wash filter used to dry chloroform in the preceding operation once with 5 mils of water, receiving latter in the separatory funnel containing the aqueous acid solution of phenetidin sulphate. Treat with successive small portions of solid sodium bicarbonate until an excess of this reagent, after complete neutralization of the sulphuric acid, persists at the bottom of mixture. Now add 60 mils of chloroform and for every 100 mg. of acetphenetidin known or believed to be present, 5 drops acetic anhydrid; shake for some time vigorously, allow to clear, then pass through cotton and a dry filter, as described for caffein, into a 200-mil Erlenmeyer. Distill over 50 mils of chloroform, make up to 60 mils with fresh solvent, and extract again. Distill over as before this time about 60 mils then make the third and final extraction. Distill the chloroform down to about 10 mils, transfer residue by pouring and rinsing with small quantities of solvent into a tared 50-mil crystallizing dish, evaporate on steam- or vapor-bath to apparent dryness, finally removing any considerable excess of acetic anhydrid by repeated additions of about 1 mil of fresh chloroform, to which has been added a drop of alcohol. The acetphenetidin will finally appear as a whitish, crystalline mass, having usually a faint acetous odor. The latter will disappear completely on standing some hours in the open, or more quickly on a vacuum desiccator over lime. The residue is weighed at intervals until it suffers no further loss.

CODEIN, CAFFEIN, AND ACETPHENETIDIN MIXTURE

Codein

Weigh out about 0.3500 gram of powdered material (if in pill or tablet form at least 10 of these should be reduced to powder), transfer to a separatory funnel by means of 10 mils very dilute sulphuric acid (or sufficient to render the solution decidedly acid after neutralization of any carbonate that may be present), extract by means of vigorous shaking with 50 mils

of chloroform. After clearing draw off the solvent, allowing it to run through a small (5.5 cm.) filter into a 200-mil Erlenmeyer. Distill off about 50 mils chloroform, using a small Bunsen flame. Extract a second and third time with same amount of solvent as first used. Allow the chloroform from each extraction to run into the Erlenmeyer, then distill off all but about 10 mils. Now add 10 mils dilute sulphuric acid (1 volume concentrated acid to 5 of water) and heat on steam-bath until the chloroform has disappeared and only about 5 mils of the acid liquid remains, then treat as directed under caffein.

Render the acid liquid in separator containing the codein sulphate neutral by the addition of solid sodium bicarbonate, wash out filter used in the proceding operation to clarify the chloroform, once with water, allowing latter to run into the separator, then reextract three separate times with 50 mils chloroform. Collect solvent as above directed in a second 200-mil Erlenmeyer, distilling off most of the liquid by the aid of gentle heat. Transfer residual chloroform to a small beaker or evaporating dish, using sufficient fresh chloroform for this purpose, heat gently over steam-bath to dryness, cool, and weigh as anhydrous codein.

Caffein and Acetphenetidin

The aqueous acid solution containing the caffein and phenetidin sulphate is transferred to a separatory funnel and treated substantially as directed in the preceding method.

SEPARATION OF ACETPHENETIDIN AND SALOL

The gross separation of the mixtures from powder, tablets, or pill preparations is most conveniently effected by judicious treatment with chloroform. The separation of the two ingredients from each other can be accomplished in either one or two ways, depending:

1st. On the acid hydrolysis of phenacetin, and salol remaining thereby unchanged, or:

2d. On the alkaline hydrolysis of salol, the phenacetin in such case being unaffected.

1st. Acid Hydrolysis

Acetphenetidin

If the sample is in pill or tablet form, ascertain the weight of 20 or more, reduce to a fine powder and transfer to a small tube or bottle which can be kept tightly closed with a cork or glass stopper. Weigh out on a small (5.5 cm.) tared filter an amount equal to or a convenient multiple of the average weight of such pill or tablet, wash with successive small

portions of chloroform, in quantity about 40 to 50 mils, sufficient at least to insure complete extraction of all phenacetin and salol present in the mixture. Collect solvent in a tared 100-mil beaker and evaporate by means of a blast to apparent dryness. During this operation the beaker may be allowed to stand on a warm plate (50–60°) without danger of undue loss of solid substance. Allow to stand twenty-four hours at the ordinary temperature in the open, weigh several times or until the weight becomes practically constant, then transfer the residue, by dissolving in and washing with sufficient chloroform, to a 50-mil lipped Erlenmeyer, evaporate solvent by means of a blast and gentle heat, add 10 mils dilute sulphuric acid (1 : 10) and digest at full bath heat until the liquid is reduced one-half. Add 10 mils water, continue digestion as before, add a second 10-mil portion of water and evaporate to 5 mils. Transfer the residual liquid pouring and washing with about 20 mils water to a separatory funnel of the Squibb type and extract in rotation with 15, 10, and 5 mils chloroform, first washing each portion as obtained with 5 mils water in a second separator to recover traces of phenetidin sulphate possibly taken up by the chloroform, finally rejecting this solvent, since it contains all the salol not carried off with the aqueous and acetous vapors eliminated during the process of digestion.

To the aqueous-acid solution of phenetidin sulphate in the first separatory funnel,—into which also the wash water from the second separator has been poured,—add small portions of sodium bicarbonate until an excess of this reagent, after complete neutralization of sulphuric acid, persists at the bottom of separator. Now add 25 mils chloroform and for every 100 mg. acetphenetidin known or believed to be present 5 drops acetic anhydride, shake for some time vigorously, then pass the nearly clarified solvent into a second separator containing 5 mils water, shake, and receive the chloroform in a 200-mil Erlenmeyer, first passing it through a small (5.5 cm.) dry filter. Of this chloroform, which contains unexpended acetic anhydride, distill off about 20 mils, return same to the first separator, augment with 5 mils fresh chloroform, and repeat the extraction, washing and filtering as before, then collecting the solvent in the Erlenmeyer and again distilling until 25 mils chloroform are obtained. With this portion, make a third and final extraction, repeating the operations of washing, filtering, and distilling to the point where about 5 mils chloroform remain in the Erlenmeyer. Transfer this chloroformic residue by pouring and washing with sufficient fresh chloroform to a tared 50-mil beaker or crystallizing dish, evaporate on a steam- or vapor-bath to apparent dryness, finally removing any pronounced excess of acetic anhydride by repeated addition of 1-mil portions of fresh chloroform to which a drop of alcohol has been added and subsequent evaporation. Allow the whitish crystalline residue of acetphenetidin to stand some

time in the open, or better, in a vacuum desiccator over lime in order to dispel the last traces of anhydride. Weigh at intervals until constant.

Salol

To ascertain the quantity of salol present in the sample, subtract the weight of acetphenetidin from the combined weight of the two ingredients determined in the early part of the procedure.

Comments and Suggestions.—Tared filters for use in this and similar work may be conveniently prepared as follows: Fold, adjust in a small short-stemmed funnel, moisten and fit carefully so that the entire rim of filter closes snugly on the glass. After drying, keep in balance case or any suitable dust-proof container, and when needed weigh on a small metal support or glass tripod. It is self-evident that all weighings with tared filters should be made as nearly as possible under comparable conditions. If, for example, the first weight is taken when the hygrometer indicates a humidity of 50 per cent, the second weighing should if possible be made under approximately similar conditions. This is indispensable when it is desired to estimate the quantity of chloroform-insoluble residue, as in preparations containing sodium bicarbonate, sugar, starch, talc, or other more or less inert material. Experience has shown, however, that a variation in humidity up to 5 per cent in the two weighings would not be productive of material error.

Before carrying out an extraction in a separatory funnel, the valve should first be " locked " with a drop of water prior to the introduction of any substance in solution, otherwise losses through capillarity may result.

All distillations should be carried out over a wire gauze or asbestos provided with a small opening and subjected to a very gentle heat, the flask being connected with the condenser by means of a small spray trap, if available, similar to the type used in Kjeldahl work.

Acetphenetidin being only moderately soluble in hot aqueous media is accordingly somewhat difficult of hydrolysis. In order to insure its complete conversion to phenetidin sulphate, special attention should be directed to the end that any visible particles of crystalline substance on the sides of flask during the early part of digestion should be gradually brought into solution by gently rotating the flask, and if necessary by the occasional addition of a few drops of chloroform.

2d. Alkaline Hydrolysis

Phenacetin

On a small tared filter as above weigh out an amount of the powdered sample containing not more than 100 mg. salol, exhaust with chloroform

as for acid hydrolysis, collecting the solvent (not more than 25 mils at one time) in a small (50-mil) Erlenmeyer. Add 10 mils 2.5 per cent sodium hydroxide solution and heat five minutes on a vapor- or steam-bath at the temperature of boiling water. At the end of this period remove and cool immediately to room temperature in running water in order to reduce to a minimum any tendency of the phenacetin to undergo partial hydrolysis. Transfer the liquid to a separatory funnel by pouring and washing with as little water as possible, finally rinsing out the flask with the first 20-mil portion of chloroform used in extraction. Extract the aqueous-alkaline solution with three 20-mil portions of chloroform, washing each portion as obtained consecutively in a second separator with 5 mils water, prior to passing through a small (5.5 cm.) dry filter into a 200-mil Erlenmeyer, from which the combined solvent is distilled down to a residue of about 5 mils. Transfer the latter by pouring and washing with sufficient fresh chloroform to a small tared beaker or crystallizing dish, evaporate the solvent on the steam-bath by the aid of a blast, cool, and weigh at intervals until constant.

Salol

Transfer both aqueous-alkaline solutions from the separatory funnels to a suitable (500 mil) glass-stoppered bottle, dilute with water to about 200 mils, run in from a burette an excess (about 45 mils N/7) of potassium-bromide-bromate, follow with 10 mils conc. hydrochloric acid, close flask and shake one minute and then at intervals over a period of one-half hour. At the end of this time add 10 mils 15 per cent potassium iodide solution, agitating the closed flask at intervals for fifteen minutes. Titrate the free iodin with standard thiosulphate (preferably N/7), previously adjusted to the standard bromin solution, 1 mil of which is equivalent to 0.002548 gram salol. From the number of cubic centimeters of standard bromin solution expended, calculate the salol on the basis of 12 atoms of bromin to 1 molecule of salol.

Comments and Suggestions.—In order to facilitate the work and minimize errors due to recharging the burettes N/7 solutions are advocated in order that the volume of the thiosulphate rquired may not exceed the capacity of a 50-mil burette.

The thiosulphate solution is standardized against pure iodin. The strength of the bromin solution may be checked if desired by the aid of acetanilid.

The reactions involved in the foregoing procedure are:

First, hydrolysis of salol to sodium phenolate and salicylate:

$$C_6H_4(OH)COOC_6H_5+3NaOH=C_6H_4(ONa)COONa+C_6H_5ONa+2H_2O$$

Phenol is attacked by bromin in excess to form symmetrical tri-bromophenolbromide:

$$C_6H_5OH+4Br_2=C_6H_2Br_3OBr+4HBr$$

while salicylic acid finally yields the same product, the tribromosalicylic acid first formed being very unstable and losing its carboxyl:

$$C_6H_4(OH)COOH+4Br_2=C_6H_2Br_3OBr+4HBr+CO_2$$

The tribromophenolbromide thereupon reacts with hydroiodic acid to yield tribromophenol and free iodin:

$$C_6H_2Br_3OBr+2HI=C_6H_2Br_3OH+HBr+I_2$$

Accordingly, 12 atoms of bromin are required for every molecule of salol.

ACETPHENETIDIN AND QUININ SULPHATE

So far as the separation is concerned the method differs in no particular from that outlined for the combination of acetanilid and quinin sulphate. In the estimation, however, the procedure as applied to acetphenetidin is materially shortened, in that the physical properties of this substance permit its being weighed directly.

Acetphenetidin

Extract with three 50-mil portions of chloroform, washing each portion in rotation in a second separator (Squibb form) with 5 mils water and passing solvent after clearing through a pledget of cotton and small dry filter into a 200-mil Erlenmeyer. Distill the chloroform from the combined extractions down to about 10 mils, transfer the residue by pouring and washing with additional chloroform to a small tared crystallizing dish, allow to evaporate spontaneously or at a moderate heat on the steam-bath, cool and weigh at intervals until the loss does not exceed 0.5 mg.

Quinin Sulphate

Follow directions as given under Acetanilid and Quinin Sulphate.

Comments and Suggestions.—In all cases where cotton is used to remove suspended moisture from chloroform as suggested in the foregoing work, the material is inserted in the outlet tube, thus intercepting most of the moisture and any suspended matter that might otherwise clog the filter.

Acetphenetidin and acetanilid are not dispensed together, but there is always the possibility that a determination of the antipyretic compounds

in a mixture of these two antipyretics may become a matter of moment. Dr. Emery has developed a method for determining both acetanilid and acetphenetidin when they occur together and also a quantitative assay of a composite of the three antipyretics acetanilid, antipyrin and acetphenetidin with caffein:

ACETANILID AND ACETPHENETIDIN (PHENACETIN) IN MIXTURES. ACETPHENETIDIN

Reagents

(*a*) **Purified Iodin.**—Dissolve 2 parts of resublimed iodin and 1 of potassium iodid in 1 of water, pour the clear solution into a large volume of water, filter and wash the finely precipitated iodin several times on a porous plate with water. Dry in the air and finally in a desiccator over sulphuric acid where it is kept in a glass-stoppered weighing bottle.

(*b*) **Standard Sodium Thiosulphate Solution.**—Dissolve 30 grams of crystallized sodium thiosulphate in water and dilute to 1 liter. Standardize this solution against the purified iodin as follows: Weigh out about 0.3 gram of the purified iodin in a small glass capsule (about $\frac{1}{2}$ inch high and $\frac{5}{8}$ inch diameter) provided with a closely fitting glass cap or stopper, and place the capsule in a 200-mil Erlenmeyer flask containing 0.5 gram of potassium iodid dissolved in 10 mils of water. After complete solution, titrate with the sodium thiosulphate solution, using 1 or 2 drops of starch solution as an indicator.

(*c*) **Standard Iodin Solution.**—Dissolve 40 grams of potassium iodid in the least possible quantity of water, add 30 grams of the purified iodin and, after solution, dilute to 1 liter. Standardize 25 mils of this solution against the standard sodium thiosulphate solution.

Determination.—(1) Place 0.2 gram of the acetphenetidin-acetanilid mixture in a 50-mil lipped Erlenmeyer flask, add 2 mils of glacial acetic acid, heat gently over a wire gauze to complete solution, and dilute with 40 mils of water, previousy warmed to 70° C. Transfer the clear liquid with two 10-mil portions of warm (40° C.) water to a glass-stoppered, 100-mil graduated flask containing 25 mils of the standard iodin solution warmed to 40° C. Stopper, mix thoroughly, then add 3 mils of concentrated hydrochloric acid, continue shaking until crystallization begins and then set aside to cool. If the ratio of acetphenetidin to acetanilid is equal to or greater than unity, crystalline scales will form almost immmediately on the addition of acid. As the proportion of acetanilid increases, however, the periodide tends to remain in the liquid state. In such cases, gentle agitation or rotation of the flask in water, warmed not to exceed 40° C., hastens the formation of crystals. When the contents of the flask are at

room temperature, fill with water to within 2 to 3 mils of the mark, mix thoroughly, and allow to stand overnight. Fill to the mark with water, mix thoroughly, allow to stand thirty minutes, filter through a 5.5 cm. dry, closely fitting filter into a 50-mil graduated flask, rejecting, however, about 15 mils of the first runnings, but reserving them for the recovery of the acetanilid. Transfer the 50-mil aliquot to a 200-mil Erlenmeyer flask and titrate with the standard sodium thiosulphate solution. Calculate the amount of acetphenetidin from the following formula:

$$\text{Acetphenetidin} = I(0.0899 \times N)$$

0.0889 = the quantity of acetphenetidin contained in 1 mil of a normal solution of this substance;

N = the normality of the standard sodium thiosulphate solution employed; and

I = the number of mils of the standard sodium thiosulphate solution corresponding to the iodin combined with the acetphenetidin.

The formula of the precipitated periodide, which constitutes the basis for the above determination, is $(C_2H_5O \cdot C_6H_4NH \cdot COCH_3)_2HI \cdot I_4$.

(2) The gravimetric determination of acetphenetidin may, if desired, be effected as follows: Filter off the periodide, preferably by suction, wash with 10–15 mils of the standard iodin solution, then transfer together with the filter to a separatory funnel, using not over 50 mils of water. Remove both free and added iodin with a few small crystals of sodium sulphite and extract the liquid with three 50-mil portions of chloroform, washing each portion subsequently into a second separatory funnel with 5 mils of water. After washing and clearing, filter the chloroform solution through a dry 5.5-cm. filter into a 200-mil Erlenmeyer flask, distill off most of the chloroform, transfer the residual solution (5 to 10 mils), by means of a little chloroform, to a small, tared beaker or crystallizing dish, evaporate to dryness on a steam-bath, cool, and weigh.

For the identification of acetphenetidin, either alone or in admixture with acetanilid, the following test will be found of value: To 1 to 2 mg. of the sample in a test-tube add a drop of acetic acid and 0.5 mil of N/10 iodin, warm the mixture to about 40° C., then add a drop of concentrated hydrochloric acid. If acetphenetidin alone is present, its periodide separates almost immediately in the form of reddish-brown leaflets or needle-like crystals. If the sample consists largely of acetanilid, the separation takes place on cooling and shaking the liquid. In the globules, which, on vigorous shaking, gradually become crystalline, this test is so delicate that as little as 0.5 mg. of acetphenetidin may, if alone, be detected in the form of its characteristic periodide.

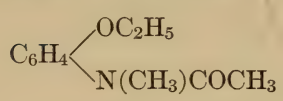
Acetanilid

(1) If the combined weight of the acetphenetidin-acetanilid mixture is known, determine that of the latter ingredient by difference; or, (2) Determine it directly from a second aliquot of the filtrate from the acetphenetidin in the foregoing as follows:

Pipette 25 to 30 mils of the clear liquid into a separatory funnel, decolorize with solid sodium sulphite and solid sodium bicarbonate in slight excess, add 1 or 2 drops of acetic anhydride, then extract with three 60-mil portions of chloroform, passing the chloroform solution, when cleared, through a small, dry filter into a 200-mil Erlenmeyer flask, and distill the chloroform, by the aid of gentle heat, to about 20 mils. Add 10 mils of sulphuric acid (1 : 10) and digest on a steam-bath until the residue has been reduced one-half, add 20 mils of water and continue the digestion for an hour: then add a second 20-mil portion of water and 10 mils of concentrated hydrochloric acid, titrate very slowly, drop by drop, with the standard bromide-bromate solution, until a faint yellow color remains. While adding this reagent, rotate the flask sufficiently to agglomerate the precipitated tribromanilin. Calculate the amount of acetanilid present.

If the preparation contains caffein or antipyrin or both in addition to acetanilid and acetphenetidin, proceed as follows: (1) Digest the mixture by heating with dilute sulphuric acid to convert acetphenetidin and acetanilid into phenetidin and anilin sulphates, respectively; (2) Separate the caffein and antipyrin by extraction with chloroform; (3) Re-form acetphenetidin and acetanilid by treating the solution of the corresponding sulphates with solid sodium bicarbonate in slight excess, then add a few drops of acetic anhydride and extract with chloroform; (4) Weigh the residue of acetanilid and acetphenetidin, then dissolve in glacial acetic acid and pour into standard iodin solution using precautions given above for precipitating the periodide of acetphenetidin. Titrate an aliquot and calculate the acetphenetidin; (5) Determine the acetanilid by difference or directly in an aliquot of the clear liquid by destroying the excess of iodin, extracting with chloroform in the presence of acetic anhydride, converting the residue to anilin sulphate by digestion with dilute sulphuric acid, and finally titrating the anilin sulphate with bromide-bromate reagent; (6) The caffein and antipyrin can be separated from each other by precipitation of the latter by picric acid.

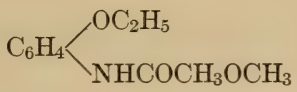
Methyl Acetphenetidin



melts 40° C., distills 300°, and crystallizes on standing. It is moderately soluble in water, soluble in alcohol, ether, benzol, and chloroform, and is used as an hyponotic.

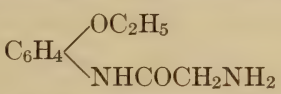
Methoxyacetphenetidin, Kryofine.

Kryofine is a condensation product of paraphenetidin and methylglycolic acid.



It is a white crystalline substance, melting 98°, slightly soluble in water, readily in alcohol.

Amino Acetphenetidin. Phenocoll or Phenamine



Phenocoll is prepared by the action of chloracetyl chloride on phenetidin and treating the product of the reaction with ammonia. It is a much stronger base than acetphenetidin and forms salts with acids.

The free base (phenocoll) obtained by precipitating the aqueous solution with fixed alkalies or their carbonates forms white, matted needles, containing one molecule of water. In its hydrated condition it melts at 95° C. while the anhydrous base melts at 100.5° C. It is stable and not chemically affected by acids or alkalies unless subjected to prolonged boiling with these reagents, by which phenocoll is split into phenetidin and glycocoll.

Phenocoll is usually dispensed or sold in the form of the hydrochloride.

Phenocoll salicylate or salocoll is prepared by neutralizing a hot aqueous solution of salicylic acid with phenocoll and cooling the solution.

It forms fine, white crystalline needles, having a sweetish taste, sparingly soluble in cold water (1 : 200), readily soluble in hot water. It gives a violet reaction with ferric chloride.

It is incompatible with soluble hydroxides and carbonates and with bodies which are incompatible with the salicylates in general.

It is used in rheumatism, gout, chorea, pleuritis, and fevers, especially in influenza.

Iodophenin is a product purporting to be a periodide of acetphenetidin. It is a brownish-black crystalline substance, melting 130–131°, and soluble in alcohol and water. It is employed chiefly for its antiseptic value, though it is claimed that it possesses some value as an internal remedy in articular rheumatism.

Thymacetin

Thymacetin is credited with the composition C_6H_2(OC$_2$H$_5$)(CH$_3$)(C$_3$H$_7$)(NHCOCH$_3$).

It is a white crystalline powder, melting 136°, soluble in alcohol and ether and slightly in water.

Phesin

Phesin is the name given to a sodium sulpho product prepared from acetphenetidin. It is soluble in water and is used as an antipyretic.

The drug trade has been flooded with a quantity of phenetidin derivatives closely allied to acetphenetidin. They differ from acetphenetidin in that some other acid radicle is substituted for the acetyl group, or the phenetidin complex is esterified with carbonic acid and another base.

Formyl Phenetidin

C_6H_4(OC$_2$H$_5$)(NHCOH)

Formylphenetidin forms colorless crystals, melting 60°, soluble in alcohol and ether but insoluble in water. It is devoid of antipyretic properties, but has been suggested as an antidote for strychnin poisoning and as an antiseptic.

Lactophenin

Lactophenin is lactylparaphenetidin,

$$C_6H_4 \cdot OC_2H_5 \cdot NH(CH_3 \cdot CHOH \cdot CO)$$

Lactophenin occurs as a white crystalline, odorless powder, of slightly bitter taste and neutral reaction. It melts at 117.5° to 118° C. It is rather difficultly soluble in cold water (1 : 330), and is soluble in 55 parts of boiling water. It is soluble in 8.5 parts of alcohol and is not precipi-

tated from this solution by water. In ether and petroleum ether it is difficultly soluble.

On boiling 0.2 gram of lactophenin with 2 mils hydrochloric acid for one minute, then diluting the solution with 20 mils water and filtering when cold the filtrate will become colored a ruby red on the addition of chromic acid solution.

On dissolving 0.1 gram lactophenin in 10 mils hot water, and filtering when cold, the filtrate on the addition of bromin water, should develop a decided turbidity which disappears on the addition of much water.

Triphenin—Propionyl-phenetidin, $C_6H_4(OC_2H_5)NH(CH_3CH_2CO)$

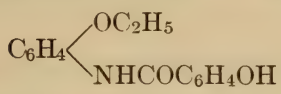
is a derivative of paraphenetidin, differing from acetphenetidin in that the acetic acid residue has been replaced by the propanoic acid residue, (CH_3CH_2CO).

It is a white, shining crystalline powder, melting at 120° C., odorless and faintly bitter. It is practically insoluble in water, requiring 2000 parts, but soluble in alcohol and ether.

In general it responds to the tests for acetphenetidin. From this it may be distinguished by its melting-point, and by identifying the propanoic acid evolved when heated with 50 per cent sulphuric acid.

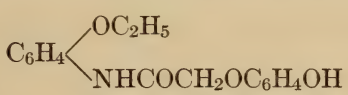
Triphenin is antipyretic, analgesic, and hypnotic.

Salicylparaphenetidin. Malakin



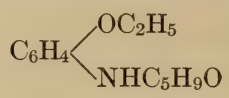
Malakin forms bright-yellow needles, melting 92° C., soluble in hot alcohol and alkali carbonates, insoluble in water. It is antipyretic, analgesic, and teniacidal, and is used in the expulsion of tapeworm.

Phenetidin Salicylacetate or Acetosalicylate, Phenosal



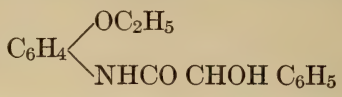
Phenosal is a white crystalline substance, melting 182°, soluble in alcohol and ether and slightly in water. It is an antipyretic, antirheumatic, and antineuralgic.

Isovalerylparaphenetidin. Sedatin



Sedatin forms lustrous, colorless needles soluble in alcohol and chloroform, slightly in ether and insoluble in water. It is used as a sedative and nervine.

Phenetidin Amygdolate. Amygdophenin



Amygdophenin forms white leaflets, melting 140–141°, soluble in ether and slightly in water. It is used as an antineuralgic.

Acetophenonphenetidin Citrate. Malarin

Malarin forms colorless crystals soluble in hot water and alkalies. Citrophen and apolysin are claimed to be compounds of citric acid and phenetidin. Both are soluble in water and are antipyretics and antineuralgics.

Hypnoacetin—Acetophenone Acetylparamidophenol Ester

$C_6H_4(OCH_2COC_6H_5)\ (NHCOCH_3)$

This body forms leaflets readily soluble in alcohol but insoluble in water, and is sometimes used as an hypnotic and antiseptic.

Eupyrin—Vanillin-ethylcarbonate-para-phenetidin

$C_6H_4(OC_2H_5)N : CH \cdot C_6H_3(O \cdot CO \cdot OC_2H_5)OCH_3)$

It occurs in light yellow, needle-shaped crystals, melting at 87 to 88° C. tasteless, with faint odor of vanillin. It is insoluble in cold water and in cold alcohol, readily soluble in warm alcohol and in ether or chloroform.

Concentrated sulphuric acid is colored by eupyrin greenish-yellow in the cold and dark brown on heating to the boiling-point.

Thermodin. Acetylparaethoxy-phenyl urethane, $C_6H_4(OC_2H_5)[(N(COOC_2H_5)(COCH_3)]$

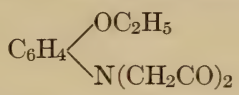
It forms colorless, odorless, and tasteless crystals, melting at 86 to 88° C. It is practically insoluble in cold water (1 : 2600); soluble in 450 parts of boiling water.

If 0.5 gram of thermodin, 5 mils sulphuric acid, and 5 mils of alcohol are mixed and warmed gently, the odor of ethyl acetate is developed. A

solution of 0.5 gram of thermodin in 5 mils of sulphuric acid on the addition of 0.2 gram of sucrose, assumes a red color, becoming more intense on standing. If 0.5 gram of thermodin is boiled with 3 mils of hydrochloric acid during one minute, then mixed with 5 mils phenol solution 1 : 20, and a solution of chlorinated lime added, an onion-red color appears which changes to blue on supersaturation with ammonium hydroxide.

Thermodin is an analgesic, antipyretic, and antiseptic.

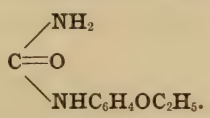
Pyrantin. Paraethoxyphenylsuccinimide



Pyrantin forms colorless needles, melting 155° C., soluble in alcohol, slightly in cold water and insoluble in ether.

A sodium salt of pyrantin is sold as Pyrantin Soluble.

Paraphenetidin Carbamide. Dulcin Sucrol or Valzin.

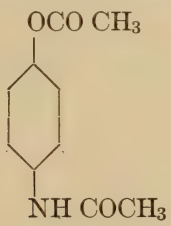


Dulcin is sweet-tasting substance, melting 173°. It is sparingly soluble in cold water, more so in hot, and readily in alcohol and ether. It is not removed by alkalies from its solution in ether and hence differs from saccharin for which it may be substituted.

Chinaphenin. Phenetidinquinin-carbonic Ester

Chinaphenin has already been described under the derivatives of quinin.

Diacetyl Paramido Phenol—Anapyralgin



This body, which is prepared by the action of acetic anhydride on paramino phenol, has a limited use as an antipyretic and analgesic, and will be found as a component of headache mixtures. It forms white

crystals, melting 118°, readily soluble in ether, alcohol, and warm water, fairly soluble in chloroform and benzol, and slightly in petroleum ether. It is removed from the aqueous solution by ether. It sublimes very slowly at the temperature of the water-bath.

The aqueous solution is neutral to litmus, it is turned a deep bronze-green color with ferric chloride, which gradually becomes brownish with increasing turbidity. It gives no precipitates with Mayer's reagent, iodin, bichromate, or potassium ferrocyanide; bromin water gives a clear solution but on standing a cloudiness appears.

When heated with concentrated sulphuric acid and subsequently treated with alcohol and warmed, the odor of ethyl acetate is evolved. Acetphenetidin when warmed with sulphuric acid, cooled, and then treated with a little water will give off an ethyl acetate odor, without the addition of alcohol. It does not give the isonitrile test.

The solution of this substance in concentrated sulphuric acid is uncolored, bichromate produces a non-characteristic olive green color and molybdic oxide a greenish blue. Concentrated nitric acid produces a violent reaction and the solution is yellowish brown. On evaporating the acid and subsequently treating with alcoholic potash there is no reaction of note.

When treated for two hours with dilute sulphuric acid 1 in 5 and then diluted, the solution does not yield a precipitate with iodin, but does with bromin water or bromide-bromate reagent. In both these reactions it differs markedly from acetphenetidin. The dilute solution reacts with ferric chloride, turning a dirty green, which darkens rapidly to a purplish brown. On neutralizing the acid solution with potassium hydroxide it becomes pale violet in color. This alkaline solution on long warming with chloroform gives a slight odor of isonitrile.

CHAPTER XXII

ORGANIC ARSENIC COMPOUNDS

From the point of view of the pharmaceutical chemist the organic compounds containing arsenic may be divided into two classes, those of definite chemical composition and those of uncertain or doubtful individual identity. Those of definite chemical composition are of course divisible into a number of different classes, depending on their structural form. To the second or uncertain class belong all those substances such as the peptonates, and those whose combination with animal acids is either dependent on some third body, or which may be readily separated into their compounds by mechanical means, and are therefore more on the order of mixtures.

The simplest organic arsenic compounds are the arsines, AsR_3, which correspond to the tertiary amines. They are obtained by treating arsenious chloride with the zinc alkyl compounds or by heating the alkyl iodides with sodium arsenite. Tertiary arsines combine directly with two atoms of a halogen, forming compounds such as triethylarsine dichloride, $As(C_2H_5)_3Cl_2$, in which the arsenic atom is pentavalent. These latter substances may be decomposed on heating, yielding a halogen derivative of a secondary arsine, $As(C_2H_5)_3Cl_2 = As(C_2H_5)_2Cl + C_2H_5Cl$, and the secondary compound will add halogens to form $As(C_2H_5)_2Cl_3$, which on heating decomposes into a dihalogen derivative of a primary arsine, $As(C_2H_5)Cl_2 + C_2H_5Cl$. The primary and secondary arsines are themselves unknown.

CACODYLIC ACID

When a mixture of equal parts of arsenic trioxide and potassium acetate is subjected to dry distillation dimethyl arsine oxide or cacodyl oxide is formed.

$$As_2O_3 + 4CH_3COOK = \begin{matrix} As(CH_3)_2 \\ \\ As(CH_3)_2 \end{matrix} \!\!>\!\! O + 2K_2CO_3 + 2CO_2$$

It is an intensely evil-smelling liquid, boiling 150° C., extremely poisonous,

and unites with acids forming salts, $As(CH_3)_2Cl$. On oxidation with mercuric oxide cacodylic acid is produced.

$$\begin{matrix} As(CH_3)_2 \\ \\ As(CH_3)_2 \end{matrix}\!\!>\!O + 2HgO + H_2O = 2(CH_3)_2AsO \cdot OH + 2Hg$$

Cacodylic acid is a crystalline, odorless, deliquescent substance, soluble in water and alcohol, and melts 200° C. It is monobasic, acid to litmus and phenolphthalein, and neutral to methyl orange. If 1 mil of the solution of the acid is treated with 10 mils of a solution of hypophosphorous acid containing hydrochloric acid, stoppered and allowed to stand, the odor of cacodyl will be noted on uncorking the flask.

The cacodyl complex is decomposed with considerable difficulty. If cacodylic acid or its salts are fused with alkali and afterward dissolved in water, acidulated, and subjected to the action of hydrogen sulphide, there is considerable precipitation of the sulphide, but the odor of cacodyl is apparent. Similar conditions will be noted in the Marsh test, the mirror forms but there is an odor of cacodyl evolved.

The cacodylates are not of great importance medicinally at the present time. They may be used in cases where an arsenic tonic is indicated, such as malaria, diabetes, anemia, chlorosis, etc., and in veterinary practice the sodium salt has been found useful as a remedy for " loco " poisoning.

A number of salts have been prepared, including the sodium, potassium, lithium, calcium, magnesium, iron, manganese, silver, and mercury. Some of these, especially with the heavier metals, are of doubtful composition; e.g., the iron salt may be simply a mixture of iron oxide and the acid.

The sodium salt is the best known commercial compound. It may contain varying amounts of water, but as marketed it usually contains three molecules.

It is a white powder, very soluble in water, forming needle-shaped crystals, hygroscopic, but otherwise of marked stability. The aqueous solution is alkaline toward litmus, but nearly neutral toward phenolphthalein.

On addition of silver nitrate to a solution of 1 gram of sodium cacodylate in 20 mils of water, a white precipitate is formed which is soluble in nitric acid and in ammonia water. If to 1 mil of a 1 per cent solution of sodium cacodylate 10 mils of hypophosphorous acid are added and put aside for one hour in a closed container, a disgusting odor of cacodyl is apparent.

If calcium chloride solution is added to a solution of sodium cacodylate (1 : 20) no precipitate will be produced in the cold nor on warming (distinction from sodium menomethyl arsenate).

Estimation.—A weighed quantity (approximately 1 gram) is dissolved in 25 mils of water, one drop of methyl orange added, and then normal

hydrochloric acid added until a faint pink color appears; 1 mil normal hydrochloric acid = 0.2125 gram of sodium cacodylate. If to the finished titration phenolphthalein is added, a volume of normal potassium hydroxide equal to the volume of normal acid used should be required to produce a red color; $(CH_3)_2AsO \cdot OH$ being a monobasic acid toward phenolphthalein.

The monomethyl acid, $CH_3AsO(OH)_2$, or arsonic acid, is known in the form of its sodium salt, $CH_3AsO(ONa)_2$, called Arrhenal or New Cacodyle, which is prepared by the interaction of methyl iodide and sodium arsenate in the presence of an excess of alkali.

Arrhenal is soluble about 1 in 1 in water, only slightly in alcohol 90 per cent. A solution of the salt (strongly acidified) with hydrogen sulphide gives a precipitate of mono- and disulphide of methyl-arsine. Arrhenal solutions do not precipitate with baryta water (sodium cacodylate does), nor with magnesia mixtures (nor does sodium cacodylate), nor by cold solution of calcium chloride (nor does sodium cacodylate), but are precipitated by nitrates of silver (white silky precipitate; sodium cacodylate none) and mercury (also sodium cacodylate; both yellow, arrhenal the darker of the two). Mercuric chloride gives reddish-yellow precipitate with arrhenal, and a white precipitate with sodium cacodylate. Sodium *p*-aminophenylarsonate gives a white precipitate with these reagents in every case. Arrhenal may be estimated by dissolving about 0.2 gram in 1 to 2 mils of water and adding 15 to 20 mils of hydrochloric and hypophosphorous acid mixture. After twelve hours dilute with 15 to 20 mils of water and filter, washing the residue with water. To the filter and its contents add a known excess of N/10 iodin solution, shake well, and titrate excess with sodium thiosulphate.

$$CH_3As + 4I + 3H_2O = CH_3AsO(OH)_2 + 4HI$$

The black body CH_3As is quantitatively produced from 1 molecule $CH_3AsO \cdot (ONa)_2$, therefore 4 atoms of iodin = 1 molecule arrhenal. Bougault suggested this reagent for testing for traces of arsenic in glycerin (arsenite or arsenate) and for cacodylate. For the latter it is exceedingly delicate.

To prepare the test, dissolve 20 grams sodium hypophosphite in 20 mils water and add 200 mils hydrochloric acid (1.17 sp. gr.). Sodium chloride is thrown out and removed. To apply the test, 5 mils glycerin is mixed with 10 mils of the reagent. Place in water-bath—brown deposit.

This methylarsine, CH_3As, is also obtainable by action of sodium hypophosphite and sulphuric acid on sodium cacodylate,

$$2H_3PO_2 + AsCH_3O(OH) = 2H_3PO_3 + CH_3As + H_2O,$$

as a yellow oil insoluble in water, with strong garlic odor.

Arsanilic Acid, $C_6H_4(NH_2)(As(OH)_2)$

Arsanilic acid is prepared by condensing anilin and arsenic acid. The sodium salt, $C_6H_4(NH_2)(AsO \cdot OH \cdot ONa)$, crystallizes with 5 molecules of water, 3 of which are lost by efflorescence. The arsenic content of the commercial article varies somewhat and the product is known by several names, Arsanin, Atoxyl, Soamin and Sodium arsanilate, all of which may differ slightly in their amounts of arsenic.

An acid solution of sodium arsanilate is not affected by hydrogen sulphide in the cold, but precipitation is complete when the solution is warmed. Iodin is liberated when a solution is treated with hydrochloric acid and potassium iodide, and the resulting solution is precipitated by hydrogen sulphide.

Mineral acids cause a precipitation of white arsanilic acid, and silver nitrate throws out a white precipitate. An aqueous solution when treated with hydrochloric acid and potassium nitrate, gives a deep red color with a solution of beta-naphthol in sodium hydroxide.

Solutions of sodium arsanilate give a yellow precipitate or a yellow color with calcium hypochlorite and a blue color with the same reagent in the presence of phenol. With reducing agents such as zinc and sulphuric acid in the cold or stannous chloride or hypophosphorous acid in strong hydrochloric acid on warming, a yellow precipitate is obtained. On conversion to arsendiazo benzene by adding a few drops of 0.5 per cent solution of sodium nitrite and a little sulphuric acid, the solution will give a carmine-red color with acetaldehyde, followed by a few drops of potassium hydroxide, and with an excess of alkali the color changes to yellow.

Arsacetin, $C_6H_4(NHCH_3CO)(AsO \cdot OH \cdot ONa) + 4H_2O$

Arsacetin is the sodium salt of a derivative of arsanilic acid. It is a white, crystalline substance, odorless, tasteless, and fairly soluble in water. The aqueous solution gives a white precipitate with silver nitrate.

If a mixture of 0.1 gram arsacetin, 0.5 gram dry sodium carbonate, and 0.5 gram potassium nitrate are melted in a porcelain crucible, the white mass dissolved in 10 mils water and the solution neutralized with dilute nitric acid, a portion of the liquid yields a white crystalline precipitate on addition of an equal volume of magnesia mixture. A further portion of the neutral liquid furnishes a brown precipitate, soluble in ammonia and also in nitric acid, on addition of a few drops of silver nitrate solution.

If 0.2 gram arsacetin is heated with 5 mils alcohol and 5 mils sulphuric acid, the odor of acetic ether is developed.

The aqueous solution of arsacetin (1 : 10) should be clear and colorless, possess at most a faintly acid reaction, and after addition of 5 mils dilute hydrochloric acid the liquid should not be altered by freshly prepared hydrogen sulphide solution.

If 0.1 gram arsacetin is dissolved in 20 mils water, 1 mil dilute hydrochloric acid and 2 drops sodium nitrite solution added and filtered, an alkaline beta-naphthol solution should produce no red coloration in the filtrate. An aqueous solution (1 : 20) to which 20 mils magnesia mixture is added should afford no turbidity or precipitate within two hours.

Five-tenths gram powdered arsacetin, after heating for four hours at 110–120° C., should show a loss in weight of about 20 per cent.

In order to determine the arsenic in atoxyl and arsacetin Rupp and Lehmann [1] heat 0.2 gram of the substance with 10 mils of concentrated sulphuric acid to 70°, and then 1 gram of potassium permanganate is added in small portions with agitation, followed by 5–10 mils hydrogen peroxide until the solution is clear. It is then diluted with 20 mils of water, boiled ten to fifteen minutes and diluted with 50 mils water. After cooling 2 grams of potassium iodide are added and after standing one hour the liberated iodin is titrated with N/10 thiosulphate.

ARSENOPHENOL-AMINES

These bodies contain two atoms of arsenic believed to be coupled together by a double linkage, the arsenobenzene, $C_6H_5 \cdot As = AsC_6H_5$, comparable with azobenzene, $C_6H_5N = NC_6H_5$.

Arsenphenol-Amine Hydrochloride. Salvarsan. Arsphenamine

This interesting body, originally exploited as Erlich's "606," is 3-diamino-4-dihydroxy-1 arsenobenzene hydrochloride

$$HClNH_2 \cdot OH \cdot C_6H_3As = AsC_6H_3 \cdot OH \cdot NH_2 \cdot HCL + 2H_2O$$

The commercial product contains 29.5 to 31.57 per cent arsenic.

It is a yellow, crystalline, hygroscopic powder, very unstable in air. It is readily soluble in water, yielding a solution with an acid reaction. The addition of sodium hydroxide solution to an aqueous solution in the ratio of two molecules of sodium hydroxide to one of salvarsan, precipitates the free base ($NH_2 \cdot OH \cdot C_6H_3As : As \cdot C_6H_3 \cdot OH \cdot NH_2$). On the addition of an aqueous solution of sodium carbonate to an aqueous solution of salvarsan, a precipitate is produced which is insoluble in an excess of the reagent.

When heated with an alkaline solution of potassium permanganate the permanganate solution is reduced and ammonia given off.

[1] Apoth. Zeit., 1911, 26, 200.

The addition of ferric chloride solution to an aqueous solution of salvarsan produces a brownish-violet color, which gradually changes to a dark red; finally the liquid becomes turbid.

Silver nitrate solution added to an aqueous solution of salvarsan acidified with dilute nitric acid yields a dark-yellow precipitate which rapidly becomes black.

The addition of concentrated nitric acid to an aqueous solution produces a yellowish-white precipitate. On further addition of the acid the precipitate redissolves and the solution becomes dark red.

Salvarsan gives a green color with nickel salts, pink with cobalt, blue with copper, and a yellow precipitate with picric acid.

Neosalvarsan—Neoarsphenamine

Neosalvarsan is a mixture of sodium 3-diamino-4-dihydroxy-l-arsenobenzene-methanal-sulphoxylate, $NH_2 \cdot OH \cdot C_6H_3 \cdot As : As \cdot C_6H_3 \cdot OH \cdot NH(CH_2O)OSNa$, with inert inorganic salts. The arsenic content of three parts of neosalvarsan is approximately equal to that of 2 parts of salvarsan.

It is an orange-yellow powder possessing a peculiar odor. It is very unstable in the air. It is readily soluble in water, yielding a yellow solution which is neutral toward litmus. Upon standing the aqueous solution becomes dark brown, forming a brown precipitate.

A freshly prepared aqueous solution (1 in 100) yields a precipitate on the addition of mineral acids, a brown color and black precipitate with silver nitrate, and with ferric chloride a violet color should be produced, which soon changes to a dark red.

If to 10 mils of the aqueous solution 5 mils of diluted hydrochloric acid are added and the mixture heated, sulphur dioxide will be evolved. If to 10 mils of the aqueous solution 5 mils of diluted hydrochloric acid are added, the precipitate collected on a filter and treated with zinc dust and warmed with diluted hydrochloric acid in a test-tube, and if paper moistened with a 5 per cent cadmium chloride solution is held in the mouth of the tube, the paper should be stained yellow within a few minutes (distinction from salvarsan).

If to 10 mils of the aqueous solution 5 mils of diluted hydrochloric acid are added, the precipitate removed by filtration, 2 mils of barium chloride test solution added to the filtrate, the mixture allowed to stand for twelve hours, the precipitate of barium sulphate removed by filtration, 5 mils of nitric acid added to the filtrate, the mixture boiled and evaporated to dryness, the residue should not be completely soluble in 50 mils of hot water slightly acidified with hydrochloric acid.

These remedies are usually dispensed in sealed tubes containing varying quantities or dosages.

Lehmann [1] recommends the following method for estimating the arsenic in salvarsan and neosalvarsan: 0.2 gram is weighed into a 200-mil glass-stoppered flask of Erlenmeyer shape (iodin-number flask), 1 gram potassium permanganate added, 5 mils dilute sulphuric acid and the mixture agitated repeatedly over a period of ten minutes. Ten mils of concentrated sulphuric acid are slowly added, rotating the flask meanwhile, followed by 5 to 10 mils hydrogen peroxide solution added drop by drop until the manganese precipitate disappears and a clear solution results. Twenty-five mils of water are now added and the solution boiled for ten minutes,[2] then diluted cautiously with 50 mils water. After cooling 2.5 grams of potassium iodide are added and the flask stoppered and allowed to stand one hour, the free iodin being titrated at the end of that time with N/10 sodium thiosulphate. One mil = .003748 gram arsenic.

GRAVIMETRIC DETERMINATION OF ARSENIC IN SALVARSAN

Meyers and DuMez [3] obtained results with this method which closely parallel those obtained with Lehmann's procedure.

Weigh out accurately about 0.2 gram of the product and transfer it to a Kjeldahl flask of 300 mils' capacity. Add 1.5 grams of a mixture of equal parts of sodium nitrate and potassium nitrate, 200 mils of distilled water and 5 mils concentrated sulphuric acid. Heat the mixture slowly under a hood to allow the escape of the nitric acid fumes. Add a small quantity of concentrated or fuming nitric acid from time to time, until oxidation is completed, which is generally indicated by the disappearance of the yellow color.[4] Continue the digestion until the volume of the liquid has been reduced to about 15 mils,[5] cool, add 100 mils of distilled water, and again concentrate to about 15 mils in order to remove the last traces of nitric acid. If the product has been completely oxidized and all traces of nitric acid have been removed, the liquid will be water-clear at this point. After cooling, cautiously neutralize the liquid with strong ammonia water and transfer it to a 300-mil beaker, using a small quantity of distilled water for rinsing the flask.

To the solution, which will now contain all of the arsenic in the form of arsenate, add 10 to 20 mils of N/2 ammonium chloride solution for every

[1] Apoth. Zeit., 27, 545.

[2] Experience has shown that ten minutes' boiling is not sufficient to remove all of the peroxide. Myers and DuMez recommend that after boiling, the last traces of peroxide be removed by the addition of a drop or two of permanganate solution (1 per cent) and the resulting pink color removed with a slight excess of oxalic acid solution.

[3] Public Health Reports, 1918, 1003.

[4] Sometimes the liquid may still have a pale yellow tint.

[5] Concentration should be effected in such a manner that the formation of sulphuric acid fumes in large quantities will be avoided.

50 mils of the liquid, then 20 mils of magnesia mixture, drop by drop, with constant stirring. Finally add an amount of strong ammonia water, equal to one-third the volume of the liquid, and 2 mils of alcohol. After allowing the mixture to stand for twelve hours, collect the precipitate, with the aid of a suction pump, in a Gooch crucible, which has been prepared as follows:

Cover the bottom of the crucible with a thin layer of asbestos, which has previously been washed with ammonia water (2.5 per cent), and dry in an oven at 110° C. Remove the crucible from the oven and place it in a larger porcelain crucible, fitted with an asbestos ring so that the sides and bottom of the two will not touch, put on the cover and heat slowly over an open flame until there is a light-red glow on the outer crucible. Remove the Gooch crucible, cool in a desiccator and weigh.

After the precipitate has been collected, dry the crucible as described above, but add a crystal of ammonuim nitrate before heating over the open flame. Finally cool the crucible and weigh. The weight of the precipitate multiplied by 0.48275 represents the amount of arsenic present in the sample taken for analysis.

Salvarsan in Forensic Testing

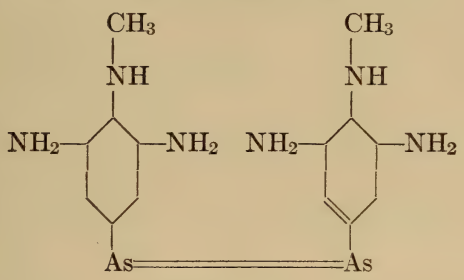
Comparatively large amounts of arsenic can be introduced into the body in the form of salvarsan without any symptoms of arsenical poisoning, and it is of importance to distinguish between arsenic in this form and ordinary inorganic arsenic in cases of suspected arsenical poisoning. Positive arsenic reactions are given with the Reinsch, Marsh, and Gutzeit tests. Penicillium glaucum gives the garlic odor, but Bettendorf's test is negative and hydrogen sulphide gives no precipitate. Ferric chloride gives an intense greenish red, auric chloride deep red momentarily; platinic chloride is gradually reduced in the cold, Nessler's reagent is reduced immediately, and phosphomolybdic acid gives an intense blue. Alpha-naphthylamine gives a deep red to violet dye, and the test may be applied directly to urine.

Salvarsan may be recovered unchanged from tissue by extraction with alcohol acidified with hydrochloric acid.

Silver chloride, bromide, and iodide, when freshly prepared, dissolve in solutions of arsenobenzene hydrochloride. A solution of silver bromide in potassium cyanide is added drop by drop to a solution of the arsenic compound until a permanent precipitate is obtained, which is then redissolved by the addition of hydrochloric acid drop by drop. From the solution thus obtained sulphuric acid precipitates the arseno-benzene silver compound in the form of an insoluble sulphate, which after being washed

free from the last traces of potassium chloride and cyanide, forms an orange to brown powder according to the quantity of silver present. It dissolves in water containing a small quantity of sodium carbonate. The chlorine compounds possess the least and the bromin the most antiseptic power and therapeutic value.

Dimethylaminotetraminoarsenobenzene



This is a new substance, yellowish green in color, which darkens in the air. It is soluble in acetone and acetic acid but only with difficulty in alcohol and insoluble in water.

Arsenoferratin. Sodium Arsenoferrialbuminate

Arsenoferratin is an arsenic iron albumin compound, obtained by introducing the element arsenic into the molecules of ferrialbuminic acid. It contains iron in the ferric state equivalent to 6 per cent metallic iron and arsenic equivalent to 0.06 per cent as metallic arsenic. It is a brown almost odorless and tasteless powder, readily soluble in water and dilute alkalies.

Arsenoferratose is a solution of this substance obtained by dissolving 5 parts in 68 parts of water with the aid of a little sodium hydroxide, 20 parts glycerin, 6 parts alcohol, and 1 part Angostura essence.

For the determination of the iron and arsenic in the solution of Arsenoferratose and applicable also for the salt the following method is recommended by the laboratory of the American Medical Association.

Twenty-five mils are evaporated to a viscid consistency in a capacious tared crucible and the residue heated in a drying oven at 100° for three hours to a constant weight. (The author doubts if it is possible to obtain a constant weight by evaporating a mixture containing this quantity of glycerin.) The weight of the evaporated residue multiplied by 4 should be about 23. Now carefully incinerate and ignite. After cooling moisten with nitric acid, ignite and finally take up with 10 mils hydrochloric acid. The solution is diluted with 30 mils of water and when cold

3 grams potassium iodide are added and the mixture allowed to stand for an hour in a well-stoppered bottle at the ordinary temperature. It is then titrated with N/10 sodium thiosulphate. The iodin liberated should require about 12.5 mils of N/10 sodium thiosulphate.

If arsenoferratose is treated as given below, and the arsenic titrated with N/10 iodin solution, the iodin consumed should indicate the presence of not less than 0.003 gram arsenic per 100 mils arsenoferratose.

Fifty mils of the arsenoferratose contained in a distillation flask of about 500-mils capacity, are heated on a water-bath and evaporated to about one-third of its original volume. To the residue are now added 80 mils of arsenic-free concentrated hydrochloric acid and 20 mils arsenic-free 25 per cent solution of ferrous chloride, and the arsenic chloride distilled over, the receiver being kept well cooled by means of cold water. The contents of the receiver are then supersaturated with sodium bicarbonate, and the arsenic titrated with the N/10 iodin solution.

Arsen-triferrin

Arsen-triferrin is an iron arsenoparanucleate containing arsenic in organic combination and standardized to contain a definite amount of arsenic by diluting with iron paranucleate. It should contain about 16 per cent of iron, 0.1 per cent of arsenic (As), and 2.5 per cent of phosphorus, all in organic combination.

Arsen-triferrin is an orange-colored, tasteless powder, soluble in dilute alkalies from which it can be precipitated by the addition of an acid. It is also soluble in about 8 per cent of hydrochloric acid on warming.

Arsenic Peptonate

Arsenic peptonate, for which no definite composition is assigned, is prepared by adding a solution of arsenic bromide in strong alcohol to beef peptone suspended in dilute alcohol, and stirring. The finished product contains about 45 per cent arsenic figured as As_2O_3.

For assaying this product pour 5 mils concentrated sulphuric acid upon 0.2 gram sample in a 200-mil beaker. Heat so that SO_3 fumes are barely given off, until the liquid becomes clear (cooling and adding more sulphuric acid in case the liquid evaporates to less than a layer $\frac{1}{8}$ inch thick before becoming clear). Dilute and neutralize the acid with sodium hydroxide. Acidify slightly. Make alkaline with sodium bicarbonate and titrate with N/10 iodin.

Each 0.4046 mil N/10 iodin represents 1 per cent As_2O_3.

If 0.2 gram sample is taken each mil N/10 iodin equals 0.004942 gram As_2O_3.

Enesol. Mercury Salicylarsenate

This is a white substance containing 38 to 39 per cent mercury and 14 to 15 per cent arsenic. It is soluble in water and is employed in syphilis.

Recently there has been reported[1] a series of new arsenic compounds prepared from a chlorarsenobehenoleic acid or chlorarsenobehenic acid. The first reports claimed the latter, but in both cases the strontium salt is called "Elarson." The acid is prepared by heating arsenic trichloride with behenic or behenoleic acid. It is a brownish-red oil, insoluble in water, but dissolving in the alkali solvents and in olive oil. The salts resemble soaps. Methyl derivatives have been prepared.

The new compounds are recommended for secondary anemia, phthisis, chorea, neuralgia, and Basedow's disease.

Elarson contains about 13 per cent arsenic, 6 per cent chlorine and 9 per cent strontium. It is a white, amorphous, tasteless powder, insoluble in water, but slightly soluble in alcohol and ether.

Elarson is broken up by boiling with alcoholic potash under a reflux. If the alcoholic liquid is diluted, a portion of the solution on treatment with dilute sulphuric acid and filtered, will give characteristic tests for arsenic and chloride. The balance of the solution, diluted with water, acidified with dilute hydrochloric acid and filtered, will yield a precipitate of strontium oxalate on treatment with ammonia and ammonium oxalate.

[1] Forshn. Therap. d. Gegenw., 54, 1. Am. 403, 106.

CHAPTER XXIII

PROTEINS AND DIGESTIVES

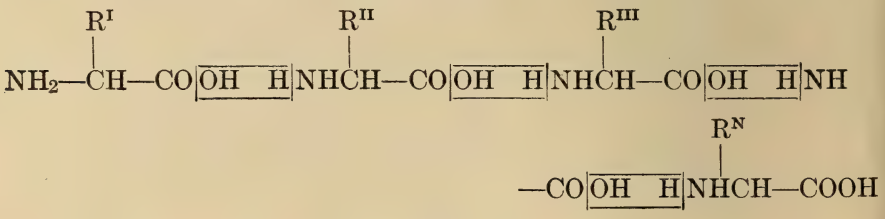
PROTEINS

THE chemistry of the proteins in so far as it affects the drug analyst is confined to those groups which occur in beef and vegetable extracts, predigested meat products, extracts of fish livers, casein, and nucleic acid preparations. A detailed account and description of all of the different classes of proteins is not essential in a work of this kind, but a brief summary of the characteristics of the important groups will enable the chemist to comprehend the fundamental status of protein chemistry.

Accompanying the proteins in beef are the xanthin derivatives, creatin and creatinin. These nitrogenous substances, though they are not proteins, are always important factors in studying meat and vegetable extracts. The xanthin bases have been described in the section on Alkaloids.

S. B. Schryver in the new edition of Allen, Vol. 8, p. 17 et seq., gives a very comprehensive résumé of the chemistry of the proteins. He classifies the proteins as follows: Simple proteins, conjugated proteins, and derived proteins. The first class include the protamines, highly nitrogenous substances; histones, also containing considerable nitrogen; albumins, water-soluble proteins of egg white and blood serum; globulins, insoluble in water and widely distributed; prolamines, soluble in 70 to 90 per cent alcohol, gliadin being an example; glutenins; scleroproteins or albuminoids. The second class include the nucleoproteins; glycoproteins; phosphoproteins; hemoglobins, and lecitho proteins. The last class include the metaproteins obtained by acid and alkaline digestion of the proteins; proteoses, peptones, and polypeptides derived by the action of enzymes and the latter also by synthesis.

The proteins differ from one another in the number and kind of amino acids which they yield on hydrolysis. They are formed by the condensation of several amino acids according to the scheme:



The hydrolytic products of the proteins thus far isolated and identified include about a score of amino acids, the simplest being glycine or amino-acetic acid, $(NH_2)CH_2COOH$. Others thus far identified are:

Alanine, alpha-aminopropionic acid, $CH_3CH(NH)_2COOH$.

Valine, alpha-aminoisovaleric acid, $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\cdot CH(NH_2)COOH$.

Leucine, alpha-aminoisocaproic acid, $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\cdot CH_2\cdot CH(NH_2)COOH$.

Isoleucine, alpha-amino-beta-methyl-beta-ethyl propionic acid.

$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>\!CH\cdot CH(NH_2)COOH$$

Phenylalanine, beta-phenyl-alpha-amino propionic acid,

$$C_6H_5CH_2CH(NH_2)COOH$$

Serine, beta-hydroxy-alpha-aminopropionic acid,

$$OH\cdot CH_2\cdot CH(NH_2)COOH$$

Cystine, Di-beta-thio-alpha-aminopropionic acid,

$$HOOC\cdot CH(NH_2)\cdot CH_2S{-}S\cdot CH_2\cdot CH(NH_2)COOH$$

Aspartic or aminosuccinic acid, $HOOC\cdot CH_2\cdot CH(NH_2)COOH$.

Glutamic or alpha-aminoglutaric acid,

$$HOOC\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot COOH$$

Arginine, alpha-amino-delta-guanidinevaleric acid,

$$NH{=}C\begin{matrix}\diagup NH_2\\\diagdown NH\end{matrix}\!\!>\!{-}CH_2\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot COOH$$

Lysine, alpha-epsilon-diaminocaproic acid,

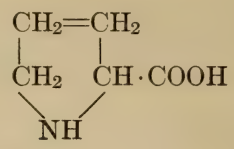
$$H_2N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot COOH$$

Caseinic or diaminotrihydroxydodecanic acid, $C_{12}H_{26}O_5N_2$.

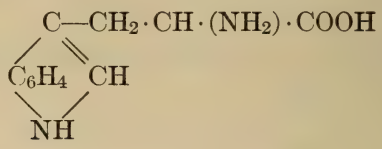
Histidine, beta-iminazole-alpha-aminopropionic acid,

$$\begin{matrix}&&CH\\&\diagup&&\diagdown\\HC&=&N&&NH\end{matrix}\!\!>\!C{-}CH_2\cdot CH(NH)_2\cdot COOH$$

Proline, alpha-pyrrolidine carboxylic acid,



Hydroxyproline, hydroxypyrrolidine carboxylic acid, $C_5H_6O_3N$.
Trytophan, beta-indole-alpha-aminopropionic acid,



The vegetable proteins belong to the albumins, globulins, glutelins, and prolamines, no representative of the remaining groups having been found.

Qualitative Reactions of Proteins.—Nitrogen and sulphur are present in proteins and may be recognized by the usual methods of detecting them in organic combination. Some water-soluble proteins coagulate on heating and others require the presence of a little acid. Strong alcoholic solutions usually precipitate. Concentrated nitric acid causes a precipitate with proteins, and potassium ferrocyanide added to a solution distinctly acid with acetic acid produces a white flocculent precipitate. Some of the alkaloidal reagents, notably phosphotungstic and phosphomolybdic acids, Mayer's reagent, potassium-bismuth iodide, tannic and picric acid, yield precipitates.

The derived proteins, especially the proteoses and peptones, are not affected by the majority of the precipitating reagents. Gelatin does not precipitate with ferrocyanide.

Aqueous solutions of proteins give, with Millon's reagent (a freshly prepared solution of mercurous nitrate with nitrous acid in solution), a white precipitate which turns brick-red on boiling, and the supernatant liquid becomes red after standing. Solid proteins turn red on boiling with the reagent. Sodium chloride must be absent when this test is performed.

Another important color reaction is the biuret test, which is obtained when a solution of an albumin or globulin is treated with a few drops of a very dilute solution of copper sulphate followed by a slight excess of fixed alkali. The blue precipitate formed by the copper will dissolve with the production of a violet color. With certain proteoses a reddish or rose color is obtained.

MEAT PRODUCTS

Beef Extract

Beef Extract is a product obtained by extracting fresh meat with boiling water and concentrating the liquid portion by evaporation, after the removal of the fat. Sodium chloride is generally added, and the finished extract is of semi-solid or pasty consistency. It should contain not less than 75 per cent of total solids, nor over 27 per cent of ash, not over 12 per cent sodium chloride, not over 0.6 per cent of fat and not less than 7 per cent of nitrogen.

Fluid meat extract has the same characteristic ingredients, but is concentrated to a lower degree.

Good meat extract contains no albumin.

Creatin is constantly present in flesh, creatinin, its dehydrated form, occurs to some extent in flesh and in larger amount in meat extracts. These two substances are therefore characteristic components of meat extracts.

Creatin, $NH : C\begin{cases} NH_2 \\ N(CH_3)CH_2 \end{cases}$

Creatinin, $NH : C\begin{cases} NH—CO \\ N(CH_3)CH_2 \end{cases}$

Meat extract contains the following substances:

Non-nitrogenous Extractives.	*Nitrogenous Extractives.*
Glycogen	Creatin
Dextrin and Sugars	Creatinin
Lactic acid	Xanthin
Inositol	Hypoxanthin
	Uric Acid
	Urea
	Carnin
	Inositic acid
	Taurin

Methods of Analysis of Meat Extracts.—The methods given are those of the Association of Official Agricultural Chemists [1] and were developed and adapted to this class of products by F. C. Cook.

The liquid and semi-liquid extracts should be removed from the container and mixed before sampling. Warming will expedite the mixing of pasty extracts. Liquid preparations often show a sediment and this should be carefully removed and mixed with the sample. If the sample is in the form of cubes, 10–12 units should be ground.

[1] Jour. A. O. A. C., 1, 1915–1916, 280.

Moisture.—Use 2 grams of powdered preparations, 3 grams of pastes and 5 to 10 grams of liquids. Dissolve the pasty preparation in water and dry with sufficient ignited sand, asbestos, or pumice to absorb the solution. The determination is made in a vacuum drying-oven at the temperature of boiling water, or in the open in a current of hydrogen. The moisture is usually expelled in five hours.

Ash.—Char a quantity of the substance, representing about 2 grams of the dry material, and burn at a low heat, not to exceed dull redness, until free from carbon. If a carbon-free ash does not result, exhaust the charred mass with hot water, collect the insoluble residue on a filter, burn till the ash is white or nearly so, and then add the filtrate to the ash and evaporate to dryness. Heat to low redness till the ash is white or grayish white and weigh.

Total Phosphorus.—Use 2 to 2.5 grams of a solid or paste and an equivalent quantity of a liquid preparation. Digest in a Kjeldahl flask with concentrated sulphuric acid and potassium sulphate. After the solution becomes colorless, cool, add 100 mils of water and boil for a few minutes. Neutralize with ammonia, cool, and precipitate with magnesia mixture. After standing with an excess of ammonia, this crude precipitate is then to be filtered off, washed with dilute ammonia, dissolved in dilute nitric acid and precipitated with ammonium molybdate. The balance of the determination follows the usual course of a phosphate analysis.

Chlorine.—Dissolve about 1 gram of the sample, prepared as directed above in 20 mils of 5 per cent sodium carbonate, evaporate to dryness, and ignite as thoroughly as possible at a temperature not to exceed dull redness. Extract with hot water, filter, and wash. Return the residue to the platinum dish and ignite to an ash; dissolve in sufficient nitric acid (1 in 10), add this solution to the water extract. Add a known volume of N/10 silver nitrate in slight excess, stir well, filter, and wash thoroughly. To the filtrate and washings add 5 mils of saturated solution of ferric alum and a few mils of dilute nitric acid. Titrate the excess of silver with N/10 ammonium or potassium thiocyanate until a permanent light-brown color appears.

Fat.—Transfer the residue from the determination of moisture to a continuous extraction apparatus and extract with anhydrous ether for sixteen hours. Dry the extract at the temperature of boiling water for thirty minutes, cool in a desiccator, weigh; continue at thirty-minute intervals, this alternate drying and weighing to constant weight.

Total Nitrogen. Gunning Method.—Place .7 to 3.5 grams, according to the nitrogen content, of the substance to be analyzed in a digestion flask (Pyrex type, 500-mil capacity). Add 10 grams powdered potassium sulphate and 15 to 25 mils concentrated sulphuric acid (.1 to .3 gram crystallized copper sulphate also may be added). Place the flask in an

inclined position and heat below the boiling-point until frothing ceases. Digest for a time after the mixture is colorless or nearly so, or until oxidation is complete. Cool, dilute with about 200 mils of water, add a few pieces of granulated zinc or pumice stone, if necessary to prevent bumping, a little phenolphthalein, and sufficient strong sodium hydroxide solution to make the reaction strongly alkaline. Connect the flask with a condenser, using a rubber stopper through which passes the lower end of a Kjeldahl connecting bulb, and distill until all the ammonia has passed over into a measured quantity of standard acid (N/2 is usually the best strength to employ) and titrate with standard alkali. The first 150 mils of distillate will generally contain all of the ammonia. Before receiving the distillate in the acid, the latter should be treated with a few drops of methyl red, which is the indicator to be used for this titration.

1 mil of N/1 acid = .01703 gram NH_3

1 mil of N/1 acid = .014 gram N

1 mil of N/2 acid = .008515 gram NH_3

Nitrogen $\times$ 6.25 = Protein (Meat, Food and Feeding Stuffs)

Nitrogen $\times$ 6.38 = Casein and Albumin

Nitrogen $\times$ 5.7 = Wheat Protein.

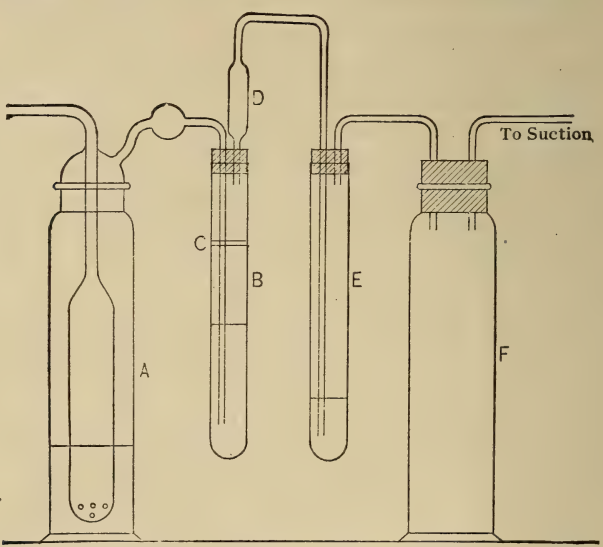
Insoluble Protein.—Dissolve 5 grams of powdered preparations, 8 to 10 grams of pasty extracts, or 20 to 25 grams of fluid extracts in cold water. Filter and wash with cold water. Transfer the filter and contents to a Kjeldahl flask and determine the nitrogen as directed above. However, if a large amount of insoluble matter is present, transfer the weighed sample to a graduated flask, make up to a definite volume, shake thoroughly, filter through a dry folded filter, and determine the nitrogen in an aliquot of the filtrate. Deduct the percentage of nitrogen in the total filtrate from the percentage of total nitrogen to obtain the percentage of nitrogen in the insoluble protein. Multiply this percentage by 6.25 to obtain percentage of insoluble protein.

Coagulable Protein.—Prepare a solution of the sample as directed above. Employ as large an aliquot of the filtrate as practicable, neutralize to phenolphthalein by the addition of acetic acid or sodium hydroxide, whichever may be necessary, add 1 mil N/1 acetic acid, boil for two to three minutes, cool to room temperature, dilute to 500 mils and pass through a dry folded filter. Determine nitrogen in 50 mils of the filtrate. Ten times the percentage of nitrogen so obtained, subtracted from the percentage of soluble nitrogen (total nitrogen minus the percentage of nitrogen occurring as insoluble protein) gives the percentage of nitrogen present as coagulable protein. Multiply this figure by 6.25 to obtain the percentage of coagulable protein in the sample.

Proteoses, Peptones and Gelatin.—Modified Tannin-Salt Method.—Use the filtrate obtained in the estimation of coagulable proteins. Transfer a 50-mil aliquot to a 100-mil graduated flask, add 15 grams sodium chloride and 10 mils of cold water, shake until the sodium chloride has dissolved and cool to 12° C. Add 30 mils of 24 per cent tannin solution, cooled to 12° C., fill to mark with water previously cooled to 12° C., shake and allow the mixture to stand at a temperature of 12° C. for twelve hours or overnight. Filter at 12° C. through a dry filter, transfer 50 mils of the filtrate to a Kjeldahl flask and add a few drops of sulphuric acid. Place the flask in a steam-bath, connect with a vacuum pump and evaporate to dryness. Determine the nitrogen in the residue. Conduct a blank determination, using the same amount of reagents and correct the result accordingly. Multiply the corrected result by 2 and deduct the amount of nitrogen as found from the amount of nitrogen determined in another 50-mil aliquot of the filtrate from the coagulable proteins without the tannin-salt treatment; the difference multiplied by 6.25 gives the percentage of proteoses, peptones and gelatin.

Meat Bases.—Deduct from the percentage of total nitrogen the sum of the percentages of nitrogen obtained in the determination of insoluble proteins, coagulable proteins, and proteoses, peptones and gelatin, to obtain the percentages of nitrogen in the meat bases. Multiply the result by 3.12 to obtain the percentages of meat bases.

Ammonia. Folin Method.—Employ the apparatus shown below. *A* is a wash bottle one-quarter full of 10 per cent sulphuric acid; *B* is a tube



containing the sample; *C* is a rubber disk and *D* is a 5-mil spray bulb to prevent spray from being carried over in the tube *E*, which contains the standard acid; *F* is a safety bottle.

Mix 1 gram of the meat extract with 2 mils N/1 hydrochloric acid, wash into tube *B* with about 5 mils of ammonia free water. Place a measured amount of N/25 or N/50 sulphuric acid or hydrochloric acid in tube *E*. Then add 1 mil of saturated potassium oxalate solution to the sample in tube *B*, introduce a few drops of kerosene and finally add just sufficient saturated potassium carbonate solution to render the mixture alkaline. Place the tubes in position at once, pass air through the apparatus and titrate the standard acid in tube *E* at hourly intervals, until ammonia ceases to be given off, using methyl red as indicator.

Proteoses and Gelatin.—Use the filtrate obtained in the estimation of coagulable protein. Evaporate to small volume and saturate with zinc sulphate (about 85 grams to 50 mils, avoiding such an excess as would later cause bumping). Let stand several hours, filter and wash the precipitate with saturated zinc sulphate solution, place the filter and precipitate in a Kjeldahl flask and determine the nitrogen. Or, if the precipitate is voluminous, make up to a definite volume with saturated zinc sulphate solution, filter and determine the nitrogen in an aliquot of the filtrate. Subtract the nitrogen thus obtained from the nitrogen in the filtrate from the coagulable protein to obtain the nitrogen of the precipitated protein (proteoses and gelatin).

Acid Alcohol-soluble Nitrogen.—Transfer 10 mils of an aqueous solution of the sample (10 grams dissolved in sufficient water to make 100 mils) or, if the sample is insoluble in water, 1 gram and 10 mils of water, to a 200-mil glass-stoppered measuring cylinder, add 1.2 mils of 12 per cent hydrochloric acid, mix and add absolute alcohol to the 200-mil mark. Mix thoroughly and set aside for several hours. Filter off a 100-mil aliquot, evaporate alcohol and determine nitrogen in the residue.

Creatin.—Dissolve about 7 grams of the sample in cold (20° C.) ammonia-free water in a 150-mil beaker, transfer the solution to a 250-mil measuring flask, dilute to the mark and mix thoroughly. Transfer a 20-mil aliquot of this solution to a 50-mil measuring flask, add 10 mils 2/N hydrochloric acid and mix. Hydrolyze in an autoclave at 117 to 120° C. for twenty minutes, allow the flask to cool somewhat, remove and chill under running water. Partially neutralize the excess of acid by adding 7.5 mils of 10 per cent sodium hydroxide solution free from carbonates, dilute to mark and mix. Make a preliminary reading on 20 mils to ascertain the volume to use to obtain a reading of approximately 8 mm. and transfer to a 500-mil graduated flask. Add 10 mils of 10 per cent hydroxide solution and 30 mils saturated picric acid solution. Mix and rotate for thirty seconds and let stand exactly $4\frac{1}{2}$ minutes. Dilute to the mark at once with water, shake thoroughly and read in a Duboscq colorimeter, comparing the color with N/2 potassium dichromate set at 8 mm.

If the reading is too high or too low (above 9.5 or below 7 mm.), calculate the quantity necessary to obtain a reading of about 8 mm. The strength of the dichromate solution used must be checked against a standard creatin solution. To obtain the values, divide 81 by the reading and multiply by the volume factor to obtain milligrams of creatinin; subtract from the combined creatinin value the equivalent of the pre-formed creatinin (determined below); this value $\times 1.16$ gives creatin, which, divided by the weight of the sample and multiplied by 100 gives the per cent of creatin.

Creatinin.—Measure about 5 mils of the solution employed above into a 500-mil measuring flask, add 10 mils of 10 per cent sodium hydroxide solution and 30 mils of saturated picric acid solution, mix and rotate for thirty seconds. Allow to stand exactly $4\frac{1}{2}$ minutes, then dilute to the mark at once with water. Shake thoroughly and read the depth of color after standing. If the reading is less than 7 or over 9.5 mm., repeat, calculating the quantity of solution necessary to obtain a reading of about 8 mm. Express the results as per cent of creatinin, making the calculations as indicated above.

Nitrates. Phenoldisulphonic Acid Method.—Reagents. Phenoldisulphonic Acid Solution.—Heat 6 grams of phenol with 37 mils of concentrated sulphuric acid on a water-bath, cool, and add 3 mils of water.

Standard Comparison Solution.—Dissolve 1 gram of pure dry potassium nitrate in water and dilute to 1 liter. Evaporate 10 mils of this solution to dryness on a steam-bath, add 2 mils of the phenoldisulphonic acid solution, mix quickly and thoroughly by means of a glass rod, heat for about one minute in a steam-bath and dilute to 100 mils. One mil of this solution is equivalent to .1 mg. of potassium nitrate. Prepare a series of standard comparison tubes by introducing amounts ranging from 1 to 20 mils of this solution (.1 to 2 mg. of KNO_3) into 50-mil Nessler tubes, adding 5 mils of strong ammonium hydroxide and diluting to 50 mils. These standard tubes are permanent several weeks if kept tightly stoppered.

Determination.—Weigh 1 gram of the sample if a solid or 10 mils if liquid, into a 100-mil flask, add 20 to 30 mils of water and heat on a steam-bath for fifteen minutes, shaking occasionally. Add 3 mils of saturated silver sulphate solution for each per cent of sodium chloride present, then 10 mils of basic lead acetate solution and 5 mils of alumina cream, shaking after each addition. Make up to the mark with water, shake and filter through a folded filter, returning the filtrate to the filter until it runs through clear. Evaporate 25 mils of the filtrate to dryness, add 1 mil of the phenol disulphonic acid solution, mix quickly and thoroughly by means of a glass rod, add 1 mil of water and 3 to 4 drops of concentrated sulphuric acid and heat on a steam-bath for two to three minutes, being

careful not to char the material. Then add about 25 mils of water and an excess of ammonium hydroxide, transfer to a 100-mil graduated flask, add 1 to 2 mils of alumina cream if not perfectly clear, dilute to the mark with water and filter. Fill a 50-mil Nessler tube to the mark with the filtrate and determine the amount of potassium nitrate present in the sample by comparison with the standard comparison tubes. If the solution is too dark for comparison with the standards, dilute with water and correct the result accordingly.

Glycerin. See pages 548–549.

Yeast Extract

Yeast on hydrolysis yields extractives similar to those obtained from meat. The water extract on evaporation darkens and acquires an odor similar to beef extract, and on superficial examination the two products appear identical. Yeast extract contains no creatin or creatinin while in a typical meat extract from 10 to 20 per cent of the total nitrogen is present in the form of these bodies. The distribution of the xanthin bases differs in meat extracts, xanthin, and hypoxanthin predominate while in yeast extracts adenin and guanin predominate. The most important test for determining the nature of the extract is the estimation of the creatin and creatinin. The analytical methods of the A. O. A. C. for meat extracts are applicable to yeast extracts.

Beef Peptone

Beef peptone is usually prepared by digesting lean beef with pineapple juce in a steam-jacketed boiler with a mechanical stirrer. When the beef is digested the liquid is strained and concentrated *in vacuo* to a thick syrup, dried, and pulverized. The product is often sold as Beef Meal and is sometimes mixed with cacao and sugar.

Beef Jelly

Beef jelly is prepared by mixing 50 parts of beef peptone, with 43 parts beef extract and 7 parts of sodium chloride.

Beef, Iron, and Wine

Beef, Iron, and Wine is a liquid preparation consisting of extract of beef or beef peptone dissolved in an hydro alcoholic solution (wine) with the aid of sodium or ammonium citrate and accompanied by iron chloride. Cinchona alkaloids, digestives, coca, and other drugs are often added to the formula.

The actual medicinal content of this class of preparations vanished to such an alarming extent at one time that the Bureau of Internal Revenue ruled that a special tax must be paid for the sale of any product having a protein content lower than 1.4 per cent. This value is a minimum for the average product made according to the National Formulary.

Cod-liver extracts when made from fresh livers probably contain some of the proteins occurring in beef extract. If made from putrid livers a number of simpler amines such as butylamine, amylamine, asellin, morrhuine, will be found. These extracts are also combined with wine beef extract, beef peptone, hypophosphites, creosote, iron chloride, and citrates.

Ruddiman and Kebler,[1] from a critical study of Beef, Iron, and Wine made according to the National Formulary, conclude that the product should possess the following characteristics: 50 mils when assayed by the Gunning method for total nitrogen should yield not less than .10 gram of nitrogen coming from the beef extract. If the amount of nitrogen obtained by the barium carbonate method exceeds .006 gram the excess is to be considered as coming from an ammonium compound and is to be deducted from the total nitrogen obtained, the remainder representing the nitrogen coming from the beef extract. Fifty mils should contain not less than .07 gram nor more than .08 gram of iron calculated as metallic iron. The percentage of alcohol should not be under 14 nor over 20.

The nitrogen determination is complicated when ammonium salts are present. The National Formulary preparation calls for sodium citrate, but many proprietary preparations are made up with ammonium citrate. Some workers determine the total nitrogen by the Gunning procedure, and then estimate the ammoniacal nitrogen in another sample by distillation with magnesium oxide, the difference between the figures obtained representing the percentage of nitrogen as beef extract.

Ruddiman and Kebler believe that magnesium oxide liberates some of the ammonia from nitrogenous constituents of the beef extract and recommend distillation with barium carbonate. Fifty mils of the sample in a 500-mil Kjeldahl flask are treated with 200 mils of water, 3 grams of barium carbonate, and a few pieces of granulated zinc or pumice. The flask is connected with the condenser in the usual way and the distillate received in N/10 acid. The ammonia liberated is considered as coming from added ammonium salts.

The developement of Folin's aëration method for ammonia previously described under meat extracts took place subsequent to the researches of Kebler and Ruddiman and is probably applicable to the Beef, Iron, and Wine products.

[1] U. S. Dept. Agri., Bu. Chem. Bull., 137, p. 194.

Nucleoproteins. Phosphoproteins

The nucleic acid of yeast is used therapeutically in combination with some of the heavy metals. The solutions of the compounds are usually antiseptic and non-irritant. The silver compound is known as Nargol and Argentose, the mercury compound is called Mercurol and the copper compound Cuprol.

Nucleic acid and nucleoproteins contain phosphorus in organic combination. They are distinguished from phosphoproteins by the fact that the latter on treatment with 1 per cent sodium hydroxide at 37° undergo hydrolysis and yield their phosphorus in the form of phosphoric acid which can be directly precipitated with ammonium magnesium chloride, whereas the phosphorus of nucleoproteins remains in organic combination when subjected to the same treatment.

Nucleic acids yield a number of substances on hydrolysis with acids; the purine bases guanin, adenin, xanthin, and hypoxanthin, cytosin, uracil, and thymin, derivatives of pyrimidin; carbohydrates and their degradation products, formic and levulinic acids; and phosphoric acid.

Casein and Vitellin

Special preparations of casein are used as concentrated foods for diabetic patients, neurasthenics, and convalescents. They are often combined with glycerophosphates, and the casein is rendered soluble by sodium bicarbonate, sodium citrate, sodium or potassium phosphate, etc. Products of the Sanatogen, Eulactol, Plasmon, Nutrose and Sanose types fall in this class. Argonin is a soluble silver casein compound which furnishes a non-irritant antiseptic useful in venereal diseases.

Casein compounds are very useful as a means of administering other medicinal agents such as lithium, mercury, silver, iron, arsenic, alkaloids, salicylates, etc.

The nomenculature in relation to casein is confusing. Casein or free casein is the base-free or uncombined protein; calcium casein or caseinate is the neutral compound that is believed to be present in fresh normal milk, the CaO being present to the amount of 1.50 per cent; basic calcium casein or caseinate is the compound consisting of casein with 2.50 per cent CaO; calcium paracasein or paracaseinate is the insoluble compound formed by the action of rennet on calcium casein; paracasein or free paracasein is the base free or uncombined protein.

Free casein may be separated from milk or its soluble compounds by precipitating with acetic or mineral acids.

The amount of casein is obtained by determining the nitrogen by the Kjeldahl-Gunning method and multiplying by 6.38.

Casein is a phosphoprotein. This class of substances is distinguished

from others by the fact that on treatment with 1 per cent sodium hydroxide at 37° for twenty-four to forty-eight hours the whole of the phosphoric acid is set free from organic combination.

Vitellin

Vitellin in combination with silver is known as Argyrol. Vitellin is a phosphoprotein of acid character which is obtained as a white granular residue on extracting egg yolk with large quantities of ether. It is soluble in saturated sodium chloride, and reprecipitated on adding an excess of water.

DIGESTIVES

The digestive ferments occupy a prominent place among modern remedial agents. The conditions under which the different ferments act are usually dissimilar; pepsin, for instance, develops its greatest digestive power at a temperature of 40° C. and in a weak acid medium, while the properties of diastase show to the best advantage in a neutral medium. While it was formerly held that a mixture of ferments could be counted upon to be active only with respect to one of the ingredients, it now appears that the value of these mixtures can be attributed to all of their components.

The commercial ferments are extractive preparations containing the enzymes which bring about the transformation of foods in the plants or animals containing them.

Proficiency in assaying digestive preparations and interpreting the results obtained can be acquired only with considerable practice. The results are always comparative, and the dynamics of the reactions are perhaps more closely connected with physiological chemistry than with those answering the laws of stable elements and compounds. Many factors influence the manipulations. Degrees of concentration should be taken into consideration. In all cases it is good practice to run parallel tests with standard products of known potency. In endeavoring to check claims of digesting value advanced on the label or in the literature of an individual product, due regard must be taken of the fact that for a long time the laboratory of every firm had its own methods of testing, and the claims were based on the results of assays by these methods.

The Proteoclastic Enzymes

The chief commercial preparations of this class are pepsin, pancreatin, and papain.

Pepsin

Pepsin is obtained from the mucous membrane of the stomach of the hog, and when purified the commercial product is a yellowish-white scale

or amorphous powder, consisting of albuminous material with varying amounts of the ferment.

Pepsin is dispensed in liquid and solid form. The liquids are usually elixirs, syrups, or wines, and are prepared with saccharated pepsin. The combinations include bismuth and ammonium citrate, ferric pyrophosphate, extract of cinchona, strychin, gentian, beef peptone, and occasionally other drugs. Pancreatin and other digestives are sometimes combined with pepsin.

Lactated pepsin is a mixture of pepsin, pancreatin, diastase, and maltose, with hydrochloric and lactic acids. This same combination with aromatic powder is sold in tablet form.

Digestive powders contain pepsin, pancreatin, bismuth subcarbonate, and aromatics. In tablets and pills pepsin will be found in combination with one or more of the other digestives, bismuth salts, gentian, charcoal, sodium bicarbonate, Nux Vomica, caffein, antipyretic drugs, Capsicum, ipecac, ginger, cerium oxalate, inspissated ox gall, salol, and cinchona alkaloids.

Pepsin is an ingredient of chewing gums. The products sold at the present time actually contain detectable quantities of pepsin, which was not the case before the activities of control legislation.

Quantitative determinations of pepsin are actually measures of the digestive power of the particular specimen under examination. Two specimens of the same appearance and weight may possess totally different potencies. The pepsin of the U. S. standard is 1–3000, which means that one part of pepsin will digest 3000 times its weight of specially prepared egg albumin at a specified temperature and within a specified period. There are no standards for products containing pepsin, and there is no way of actually measuring the quantity of pepsin present, unless a declaration on the label indicates that a certain amount of pepsin of a definite potency has been used. In the latter case a measure of the digesting power will furnish an approximate idea of the quantity used. Preparations containing pepsin, especially those of liquid nature, are subject to fairly rapid deterioration, and while they may be potent as remedial agents when freshly made, they will often be inert after a few months or even weeks unless preserved under special rigid conditions which are generally impracticable from a commercial and household standpoint.

Determination of Proteolytic Activity

U. S. P. Method for Pepsin.—Mix 25 mils of normal hydrochloric acid V. S. with 275 mils of distilled water and dissolve .1 gram of pepsin in 150 mils of this liquid. Immerse a hen's egg, which is not less than five nor more than twelve days old and has been kept in a cool place, in boiling water during fifteen minutes. As soon as the egg has sufficiently

cooled to handle it, remove the pellicle and all of the yolk; at once rub, the albumen through a clean, dry hair or brass, No. 40, sieve, reject the first portion that passes through the sieve, and place 10 grams of the succeeding portion in a wide-mouthed bottle of 100 mils' capacity. Immediately add 2 mils of the acid liquid and, with the aid of a rubber-tipped glass rod, moisten the albumen uniformly. Again add 2 mils of the acid liquid, repeat the manipulation with the glass rod, and with gradually increasing portions of the acid liquid, until the total amount added measures 20 mils. Thoroughly separate the particles of albumen from each other, rinse the rod with 15 mils more of the acid liquid, and, after warming the mixture to 52° C., add exactly 5 mils of the solution of pepsin. At once cork the bottle securely, invert it three times, and place it in a water-bath that has previously been regulated to maintain a temperature of 52° C. Keep it at this temperature for two and one-half hours, agitating the contents every ten minutes by inverting the bottle once. Then remove it from the water-bath, pour the contents into a conical measure having a diameter not exceeding 1 cm. at the bottom, and transfer the undigested egg albumen which adheres to the sides of the bottle to the measure with the aid of small portions (about 15 mils at a time) of distilled water, until the total amount used measures 50 mils. Stir the mixture well and let it stand for half an hour; the deposit of undissolved albumen does not then measure more than 1 mil.

The relative proteolytic power of pepsin, stronger or weaker than that just described, may be determined by ascertaining through repeated trials the quantity of the pepsin solution, made as directed in the assay, required to digest, under the prescribed conditions, 10 grams of boiled and disintegrated egg albumen. Divide 15,000 by this quantity expressed in mils to ascertain how many parts of egg albumen one part of Pepsin will digest.

Method for Liquid Pepsin.—Chestnut has developed a method for determining proteolytic activity which in skilled hands has given excellent results.

Preparation of Sample.—Add to 50 mils of the liquid under examination the requisite quantity of either N/10 HCl or H_2O or both, to make the preparation of N/10 acid strength when diluted with N/10 HCl to 90 mils. Preserve the sample in a refrigerator.

Preparation of Reagents. 1. *Standard Pepsin.*—Powder a good grade of acid soluble U. S. P. pepsin and pass it through a No. 60 sieve; dry *in vacuo* over H_2SO_4, pass again through a sieve and preserve in a stoppered bottle over H_2SO_4. The exact pepsin equivalent of the dry powder must be ascertained by the U. S. P. process, and this may be expressed in percentage based on the supposition that the U. S. P. product is 100 per cent pure.

2. *Pepsin Solutions.*—Weigh off definite amounts of the standard pepsin from a weighing tube into the requisite quantity of N/10 HCl to make,

2*a*: A 1 per cent solution.

2*b*: A .1 per cent solution.

These should be freshly prepared, since weak solutions of pepsin in N/10 HCl suffer decomposition on standing .

3. Add 1 mil of N/10 HCl to 9 mils of the sample.

3*a*. Immerse a stoppered flask containing 45 mils of the sample and 5 mils of N/10 HCl in boiling water for fifteen minutes and filter.

3*b*. Immerse a stoppered test-tube containing 18 mils of solution 3 in boiling water for ten minutes, and after cooling, add 2 mils of solution 2*a*, and filter if necessary.

4. *Ricin Solution.*—The cheap commercial "Ricin Praparatnach Jacoby" manufactured in Germany is ground to a No. 60 powder, thoroughly mixed and dried, and then stored in a desiccator. Digest 1 gram of this powder for one hour at 37.5° C. in 100 mils of 5 per cent of NaCl solution, cool and filter.

Method.—To each of fifteen tubes first add, from a burette, 2 mils of the ricin solution and a half mil of N/10 HCl. Heat to 37.5° C. and then add the quantities of solutions Nos. 2*b*, 3, 3*a* and 3*b*, indicated in the following tables. Measure off solutions 3*a* first and then pour in the solutions to be tested as rapidly as possible from graduated pipettes, taking note of the total time consumed in the process and beginning first with tube No. 1 and then following in natural sequence.

Sample Tables

No. of tubes	1	2	3	4	5
No. of mils 3 added	0.	.25	.50	.75	1.00
No. of mils 3*a* added	1.	.75	.50	.25	0.00
Time of digestion in minutes.	No digestion	68	42	28	19

Series II

No of tubes	1	2	3	4	5
No of mils 3*a* added	1.	.75	.50	.25	0.00
No. of mils 3*b* added	0.	.25	.50	.75	1.00
Time of digestion in minutes.	No digestion	68	42	28	19

Series III

No. of tubes	1	2	3	4	5
No of mils N/10 HCl	1.	.75	.50	.25	0.00
No. of mils 2*b*	0.	.25	.50	.75	1.00
Time of digestion in minutes.	No digestion	98	42	28	19

If the solutions to be tested are not clear they should be filtered repeatedly through a hardened filter. If, however, it be found that they cannot thus be clarified, check tubes for comparing the end digestion products should be made containing the varying amounts of the preparation made up with N/10 HCl in place of ricin.

After the addition of the solutions to be tested, the test-tubes are immersed in the 37.5° C. bath at once, preferably placed in corresponding order in a partitioned square or oblong wire rack, such as is used in bacteriological work. The tubes are shaken and examined from time to time for one or two hours, or overnight in the case of very weak solutions. The time of beginning the digestion and also the time in minutes of complete digestion for each tube should be noted (preferably with a stop watch) as indicated in the tables above given.

If the rate of digestion is the same in each series 3 contains exactly .1 per cent of pepsin, the amont present in the original solution being .2 per cent. If the rate is more rapid in I than in II or III it is stronger, the comparative strength being closely indicated by the time of action in the tubes containing less of the solution. If the rate of clearing is most rapid in III, the solution contains some substance which interferes with the action of the pepsin, and this must be removed in some way as by dialysis [1] or evaporation *in vacuo* or at a low temperature until, upon reexamination, and further dilution or concentration, the rate of digestion is identical or nearly so in each series. One mil of 2*b* represents .001 gram of pepsin.

Smaller quantities of pepsin may be determined in the same way by comparing with more diluted solutions of standard pepsin. As small a quantity as .00005 gram of U. S. P. pepsin can thus be readily detected by its nearly complete solvent action on the ricin ppt. inside of two hours and .000005 gram shows marked action on the ricin inside of the same time. After four hours' digestion, the absence of any appreciable solvent action, as judged by ocular inspection, indicates the absence of pepsin. The results should be expressed in per cent calculated on the basis of pepsin of U. S. P. quality, being 100 per cent.

The proteolytic value of pills, tablets, powders, and liquid preparations containing pepsin may be determined by following the general directions recommended in these methods. In all cases due regard must be taken of the reaction of the solution before it is added to the egg albu-

[1] Dialysis tubes are made by pouring collodion into test-tubes or small Erlenmeyer flasks allowing it to dry a little, adding more collodion and drying again two to five minutes or until the collodion does not adhere to the finger when touched, and then removing the film and the glass and plunging it at once into water. The films should be kept moist until used. The special advantage of these tubes is that they are eminently adapted for quantitative work.

men. If alkaline it should be neutralized and rendered slightly acid with dilute hydrochloric acid. The presence of preservatives and inhibitory substances must be determined.

Papain

Commercial papain consists of the inspissated juice of the Carica papaya or paw paw, usually mixed with starch and sometimes the juices of other vegetable growth, some of which have been found to be extremely toxic. Commercial papain is sometimes adulterated with pepsin and while pepsin is probably more valuable as a digesting agent, its admixture with paw paw juice and sale at an exorbitant figure for papain is not to be commended.

The ferment of papain acts best in a slightly alkaline media. It may be concentrated from the dried juice by dissolving it in water, dialyzing, and precipitating with alcohol. Papain either in the crude or concentrated form is used in the preparation of a limited number of digestive products. In the tropics the juice is used by the natives in the treatment of eczema, warts, intestinal worms, ulcers, and many kinds of foul sores, and in diphtheria to dissolve the false membrane in the throat. Its greatest use, however, is for the purpose of rendering tough meat tender. In this respect paw paw juice possesses the property of pineapple juice, the latter being largely employed in the preparation of beef peptone.

In testing papain and the preparations containing it the following method of Rippetoe [1] is recommended:

Prepare egg albumen as directed under pepsin assay U. S. P. 9th revision. Introduce into a 4-oz. wide-mouth flint bottle 40 mils of a .1 per cent sodium hydroxide solution and add 10 grams of the disintegrated albumen; stopper the bottle and shake vigorously until the albumen is broken up. Then add the papain in fine powder and mix by shaking gently for fifteen seconds. Place the bottle in a water-bath for six hours, removing the bottle every ten minutes and shaking gently for fifteen seconds. At the end of this period transfer the mixture to a 100-mil graduated stoppered cylinder, rinse the bottle with water, add the rinsing to the mixture and make the volume up to 70 mils with water. Set the cylinder aside and after standing for one hour read off the volume of the deposit. The deposit may be read a second time after standing sixteen to eighteen hours (overnight), which seems to give more positive results, especially if the volume is large.

The method is also applicable for determining the digestive value of pineapple juice. A sample of dry pineapple juice, using 1 gram of dry juice, neutralized with sodium hydroxide, added to 10 grams of the

[1] Journal of Industrial and Engineering Chemistry, 4, 1912, 517.

albumen in 35 mils .1 per cent sodium hydroxide solution, with three hours' digestion, left a residue of 2 mils, reading after eighteen hours, while a blank read 41 mils.

Shelly [1] suggests the following modification of Sorensen's test for assaying papain. Four grams casein (Hammerstein) are dissolved in 100 mils of alkali solution containing 4 mils N/1 sodium hydroxide. To 25 mils of this solution are added 25 mils water containing .1 gram dried juice and the mixture digested in an incubator at 37° C. for four hours. To 20 mils of the liquid are added 10 mils of a 40 per cent formaldehyde solution just neutralized with N/5 sodium hydroxide. This mixture, equivalent to .04 gram of sample is titrated with N/5 sodium hydroxide, using phenolphthalein, and at least 1 mil should be required to neutralize the amino acids formed, after subtracting the amount required by a similar mixture without the juice.

Thorburn's Method.[2]—.4 gram of papain and .75 gram sodium bicarbonate are dissolved in 100 mils of distilled water and heated to 50–55° C. Lean round steak is scraped to a pulp, rejecting gristle, fat, etc.; 10 grams are placed in a 200-mil digestion flask, the papain-sodium bicarbonate solution added and digested for four hours, maintaining a temperature of 50–55°. The flask is shaken every ten minutes and at the end of the digestion the contents of the flask are poured into a measuring cylinder and allowed to stand at rest for one-half hour. Not more than 10 mils of residue should remain. A blank digestion of the meat pulp and bicarbonate should be run simultaneously with the papain digestion. After reading the volume of the residue, the mixture is warmed to 50–55° 1.5 mils concentrated hydrochloric acid is added and again digested for four hours, shaking at ten-minute intervals. At the end of this period the volume of the residue should be less than 3 mils.

Pancreatin

Much has been written concerning the ferments of the pancreas and the activity of commercial pancreatin preparations. The characteristic ferments of the pancreas include amylopsin, a starch digestant, trypsin. a protein digestant, and steapsin, a fat-splitting lipase.

Pancreatin is extracted from the pancreas of the hog by water or very dilute acid, the solution precipitated by means of alcohol, and the precipitate dried at 40° C.

Pancreatin is used as a medicinal agent in a form representing a commercially high concentration of the active ferments, such as pancreatin pure and saccharated pancreatin. It is made up with pills and tablets

[1] Analyst, 39, 170.

[2] J. Amer. Pharm. Assn., 1915, 4, 224.

alone and with other ferments, with inspissated oxgall, Nux Vomica, Taraxacum, colocynth, bismuth salts, aromatics, salol, etc. Enteric pills of pancreatin are coated with keratin or salol, these agents being supposedly undissolved in the stomach, but allow the pills to pass into the intestine, where it is disintegrated by the alkaline medium, and the digestive made available. Pancreatin is an important remedy in intestinal indigestion.

Liquid pancreatin preparations are usually in the form of elixirs, and may contain pepsin, bismuth and ammonium citrate, strychnin, rhubarb, Hydrastis, and other tonics and stomachics. Pancreatin is also combined with malt extract.

The amylolytic value of pancreatin and its preparations is determined as follows:

Method for the Routine Valuation of Diastase Preparations, by W. A. Johnson.[1]—A standard starch paste is prepared from potato starch which has been purified by washing with water, and dried firstly for three hours in a current of air, and subsequently for four hours at 80° C., so as to contain 90 per cent of anhydrous starch; 22.22 grams of this starch (=20 grams of anhydrous starch) are mixed with 100 mils of cold water, and the mixture poured into 800 mils of boiling water, boiled for ten minutes, and made up to 1000 grams. In each test 50 grams of the paste are used in 250-mil flasks clamped in a water-bath kept at 40° C., and ten minutes is fixed as the time of action. In the case of liquid malt extracts, about 10 mils diluted to 100 mils are used, while 200 to 500 mg. of dry preparations in 100 mils of water are usually suitable quantities. Definite quantities of these dilute liquids (say 1 mil to 6 mils) are added to the flasks containing the starch paste, and after about eight minutes, a few drops are tested with iodin solution (2 grams of iodin and 4 grams of potassium iodide in 250 mils). The test is repeated with 100 mils of starch paste in the different flasks, just as in Lintner's method of determining diastatic activity, new limits being found between which the real value must lie, and in every case the disappearance of all color is taken as the end-point. In expressing the results in starch-converting power, allowance should be made for the fact that the statements of the manufacturers appear to be based upon results obtained with commercial starch which contains about 15 per cent of water.

The tryptic energy of pancreatin is determined as follows by the method of Field and Gross:

A casein solution of .2 per cent strength is prepared by dissolving 100 mg. of pure casein in 2 mils of N/20 sodium hydroxide, by aid of very gentle heat, and diluting to 50 mils. A dilute acid is prepared with 50 mils of alcohol, 49 mils of water and 1 mil of 100 per cent acetic acid.

[1] Jour. Am. Chem. Soc., 1908, 30, 798.

The trypsin solution is made by dissolving in the proportion of 20 mg. to 50 mils of water.

Six portions of the casein solution of 5 mils, each containing 10 mg. of casein, are measured out, and diminishing portions of the ferment solution are transferred to test-tubes, but always made up to 5 mils. For the milligram of casein the weights of ferment may be taken as follows: 2 mg., 1.3 mg., .8 mg., .5 mg., .3 mg., and .1 mg. The series of test-tubes containing casein and ferment so charged are incubated one hour at 40° C. and then withdrawn from the bath. To each tube 3 drops of the dilute acetic acid are added. If full digestion has taken place the acid fails to produce a precipitate. The last tube in which no precipitate is formed gives an approximate measure of the digesting power of the ferment, which may be sufficient.

A closer result may be obtained by making up a new series of ferment solutions of just one-tenth the strength of the last. These are to be incubated with the casein solution in the same way, the final tests being made as before.

When tested in this manner, 1 part of trypsin should digest at least 75 parts of casein.

Method for Determining the Tryptic Value of Pancreatin, C. F. Ramsay.[1]—The materials required for the test are as follows: .5 gram pancreatin added to sufficient distilled water to make 50 mils of solution; 900 mils of milk containing 1.8 grams of sodium bicarbonate; 2 grams of rennin (1 : 30,000 in ten minutes or equivalent) and 1 mil of 6 per cent acetic acid (U. S. P.) added to 50 mils of distilled water.

After warming the milk, place exactly 50 mils in a cylindrical tube of about 100-mils capacity. Prepare several such tubes and place in a water-bath, maintaining the temperature at 40° C. Add to the tubes of milk the following amounts of pancreatin solution:

Mils	
8.33	(1 : 600)
7.69	(1 : 650)
7.14	(1 : 700)
6.66	(1 : 750)
6.25	(1 : 800)

In each case note the exact time when the pancreatin is added, mix well, and after digesting fifteen minutes place 5 mils of the digested milk in a test-tube, add 3 mils of the rennin solution, and shake well. No precipitate indicates that the casein has all been peptonized and that the pancreatin is stronger than the strength tested. For example, if there was no precipitation at 1 : 700, but there was a precipitation at 1 : 750,

[1] Jour. Ind. and Eng. Chem., 3, 1911, 823.

then it would be necessary to run more digestions between 1 : 700 and 1 : 750. Make a fresh solution of pancreatin and use the following amounts:

Mils	
7.04	(1 : 710)
6.94	(1 : 720)
6.84	(1 : 730)
6.75	(1 : 740)

In this manner it can be determined quite accurately how many times its own weight of milk a given sample of pancreatin will peptonize. In order to get accurate results the test must be carried out strictly in accordance with directions. As stated above, acid will precipitate peptonized milk, therefore just enough acid is added to the rennin solution so that 3 mils of this solution will neutralize the sodium bicarbonate in 5 mils of the peptonized milk. Then the rennin will do its work, for it will not form the precipitate in an alkaline solution.

Attention must be called to the fact that pancreatin in a neutral solution deteriorates quite rapidly. Therefore this solution should be made up the last thing, so it can be added immediately to the milk. The amount of pancreatin solution suggested is sufficient for testing the strengths as indicated.

Determination of Milk-Curdling Properties.—.16 gram pancreatin and .65 gram sodium bicarbonate are placed in a 500-mil flask or bottle, 50 mils water at a temperature of 45° C. are added, the whole well shaken and allowed to macerate fifteen minutes. While this is going on 250 mils of fresh milk are warmed to 45° C. and, at the end of the maceration period, added to the pancreatin solution, mixed and maintained at 45° for one and one-half hours. The container is gently agitated from time to time during the first half hour to disintegrate the curd and at the end of this time there should be no appreciable curd. At the expiration of one and one-half hours there should be no appreciable curdy mass.

No quantitative methods have been reported for determining the lipase action. Mellanby and Wooley have determined that steapsin is very unstable. In alkaline solution at 40° it decreases 10 per cent an hour, 50°, 50 per cent an hour and at 60° is completely destroyed in five minutes. In the acid solution its destruction depends on the H ion concentrate. It is stable in the presence of large quantities of the higher fatty acids, but is destroyed quickly by small amounts (.02 NHCl) of free mineral acids. It is rapidly destroyed by trypsin. Serum or egg albumin protects steapsin from trypsin in activating pancreatic juice because of the presence of anti-trypsin in them. The action of steapsin is accelerated by bile and bile salts, but unaffected by electrolytes such as neutral salts.

Bauer,[1] in reporting some experiments performed with pancreatin on free fat, describes a process which might be useful in a study of the lipase action.

In using these preparations they are first formed into a homogeneous paste with water, which is then mixed with the fat to be hydrolyzed in the proportion of about 5 per cent. When the oil or melted fat is mechanically stirred with the paste, emulsification soon occurs. After thirty minutes to one hour, 5 per cent sodium carbonate solution is gradually added, the addition being so regulated that the emulsion when tested with red and blue litmus paper always produces a violet stain on each. After about one to two hours the requisite amount of alkali (corresponding to about 25 per cent of the fatty acids) will have been added, and the mass will usually have become too thick from the separation of fatty acids for the stirring to be continued. The mass is then left to itself. After five hours from 60 to 80 per cent of the fat will usually have been hydrolyzed, and the hydrolysis will be complete in one to four days. In one of the typical experiments quoted, 100 grams of ox-tallow were melted and mixed at 40° C. with 6 grams of pancreas powder made into a paste with 60 mils of water. The mass was stirred for an hour at 35° C., after which 80 mils of N/1 sodium carbonate solution were added little by little. After five hours 66 per cent of the fat had been hydrolyzed, and the reaction was complete in four days.

If hydrolysis ceases after a time when pancreas-lipase is allowed to act on a fat (almond oil), this is due to an alteration of the activity of the enzyme; further hydrolysis takes place if a fresh quantity of pancreatic juice be added, and sometimes, also, on addition of a fresh quantity of the fat. The hydrolysis of fat by fresh active pancreatic juice is accelerated, but not increased, by addition of bile. The hydrolysis is completed more rapidly if the pancreatic juice be added in successive portions; in this case, addition of bile does not accelerate the hydrolysis, but indeed sometimes retards it.

There are a number of commercial preparations of the pancreas gland which contain larger quantities of the ferments, or at least show greater digesting power, than the standard pancreatin of the Pharmacopœia. Some of these have received distinctive names such as Holadin, Panase. Some firms claim to have succeeded in concentrating a trypsin comparatively free from other digesting agents, which has a proteolytic value considerably greater than pancreatin. These products are usually designated as Trypsin with the name of the manufacturer hyphenated.

Much criticism has been directed toward those manufacturers who offer digestive preparations containing simultaneously pepsin and pancreatin, but the results of recent experiments seem to indicate that these

[1] Soc. Chem. Ind., 29, 1909, 149.

ferments exercise no destructive action upon one another, and that with the proper degree of acidity they can be kept in the same solution permanently for two and one-half years at least, the loss of activity noted by other observers having been due entirely to the reaction of the solution and to the degree of such reaction. Solutions containing 10 per cent each pepsin and pancreatin, containing HCl in graduated strength, from .075 to .65 per cent volume absolute, after two and one-half years, have retained their full pepsin activity. Those containing less than .35 per cent have retained their full trypsin activity, and those of .075 per cent have retained in full the amylopsin activity with that of the trypsin and pepsin.

Pepsin and pancreatin can be administered in such a solution, or mixed together in dry form, in all proportions, and the pepsin will retain its full proteolytic power and the pancreatin both its full amylolytic and tryptic activity, which latter is developed after passing the stomach and becoming mixed with the alkaline secretions of the intestine.[1]

AMYLOCLASTS

The chief starch-converting products of medicinal importance are diastase, malt extract, and pancreatin. The latter has already been considered. The commercial diastases are more or less concentrated forms of the enzyme, which are prepared either by growing the fungus on wheat bran and extracting with water, or by extracting malt, concentrating the aqueous solution under reduced pressure, and precipitating with alcohol. The crude diastase is then dried, or if a liquid preparation is desired, it is made up with the filtered precipitate.

Diastase is used alone for the treatment of ailments arising from faulty digestion of starch, and is dispensed in tablets, capsules and in liquid form. It is also combined with other digestants in general remedies for dyspepsia.

The activity of diastase products is determined by measuring the amount of maltose produced in an excess of soluble starch, or by the power of the enzyme to form products which no longer give a color with iodin solution. Both of the methods can be used with diastase, but the former is unsatisfactory for malt extracts because of the relatively small amount of active enzymes present admixed in the first place with a considerable quantity of maltose. The second method is the simplest and most rapid, and is the one generally employed in commercial work. The success of the operation depends on the close adherence to details, and these are well emphasized in the method of Francis which was originally worked out for testing Taka-Diastase.

[1] A. Zimmerman, Jour. Ind. and Eng. Chem., 3, 1911, 751.

Taka-Diastase Test, 1-150 in Ten Minutes. *Solution for Diastase.*—Weigh out very accurately .1 gram diastase. Transfer to a small mortar containing a small quantity of water and grind the mixture. Transfer to a 75-mil measuring flask, washing out the mortar very carefully, the washing being poured into the flask and adjusted to 75 mils.

Ten mils of the above solution (containing .133+ gram of diastase) will convert 150 times its weight (2 grams) of starch into hydrolyzed derivatives in ten minutes.

Standard Iodin Solution.—Dissolve 2 grams of pure iodin in q. s. H_2O containing 4 grams KI and adjust to exactly 250 mils.

For the test dilute 1.5 mils of the solution to 1000 mils with distilled water. Fill this dilution into 2-ounce clear vials, putting 50 mils (measured by means of a measuring flask) into each. Place vials on a white porcelain slab. (The strong solution of iodin should be kept in a green or amber bottle in a dark place.)

Starch Paste.—Pour about 900 mils of distilled water into a tared vessel (preferably copper) and bring to vigorous boiling. Into this pour slowly 20 grams starch suspended in about 30 mils of cold distilled water, stirring vigorously. Stir well and continue to boil for ten minutes so as to produce a homogeneous thin jelly (use only absolutely neutral potato starch). Place container and starch paste on balance (with tare) and add distilled water q. s. to adjust weight of starch solution to exactly 1000 grams. Cool with vigorous stirring to 40° C. If paste is not absolutely uniform discard it, as lumps invalidate the test.

Provide a sufficient number of cylindrical glass tubes, into which, after counterbalancing, pour exactly 100 grams starch paste. Nearly immerse the tubes of paste fitted with rubber stoppers in a water-bath at 40° C. and allow to stand until contents have attained this temperature; after which the digestive solution is added and test begun.

Water-bath.—In order to have an even temperature it is best to arrange a metal water-bath containing a perforated rack. Put in the proper measure of water and keep at a temperature of 40° C. by means of a gas burner. Large flat-bottomed tubes are best suited for containing the starch solution, but vials of any kind having wide mouths can be used.

Digestion.—Add 10 mils of the diastase solution accurately measured with pipette to starch solution in the tube, close the tube by means of a tightly fitting rubber stopper and shake vigorously, meantime note the minute and second at which shaking began. Place in water-bath and allow digestion to proceed, shaking the tube occasionally to prevent the formation of a ring of starch around the upper surface of the liquid, which does not digest so rapidly and interferes with the end reaction.

At the end of ten minutes' digestion fill a medicine dropper with the digested solution and drop two drops into one of the iodin vials. Agitate

the contents of the vial; no blue color indicative of starch should be produced.

Method of Sherman, Kendall, and Clark.—The starch paste is prepared as follows: Enough clean air dry potato starch to contain 10 grams of water-free substance is suspended in about 100 mils of cold distilled water; enough more distilled water to make one liter is poured into a 2- to 3-liter flask immersed in a brine bath and connected with a reflux condenser. The bath is then heated and if the water boils the heating is stopped so that the water may cool somewhat, then the suspension of starch is poured very carefully into the hot water, the heating resumed and the paste boiled two hours under the reflux condenser. This long boiling renders the starch paste less viscous, more homogeneous and transparent, and more easy of digestion by the amylase.

In order to determine how long the boiling of the starch paste should be continued, experiments were made in which 250-mil portions of the paste were treated with 40 mg. of taka-diastase No. 2 dissolved in 20 mils of water and the time required for digestion to products giving no color with iodin was determined as follows: Boiled one-half hour, required fifty minutes; one hour, required forty-six minutes; one and one-half hours, thirty-six minutes; three hours, thirty-three minutes; six hours, thirty minutes. Hence boiling beyond one and one-half hours had little effect upon the digestibility of the stach as thus determined. Moreover, it was noted that up to two to three hours the solutions remained colorless while on three to six hours' boiling they became slightly yellowish. Two hours was therefore decided upon as the best length of time for boiling the starch paste.

The paste at a temperature not above 40° is weighed out in 250-gram portions (equivalent to 2.5 grams anhydrous starch) into Erlenmeyer flasks of 350-400 mils' capacity and immersed in a water-bath kept at 40°. The desired amount of enzyme is then introduced along with 20 mils of water (in which the enzyme may be dissolved, or which may be used to wash it into the flask), the contents of the flask well mixed and the temperaature of 40° carefully maintained. The digestion is considered completed when .25 mil of the contents of the flask removed and mixed with 5 mils of the dilute iodin test solution [1] in a test-tube shows, when viewed against a white background, no color which can be distinguished from that of the untreated iodin test solution. The experiment is repeated with different amounts of enzyme, if necessary, until that amount is found which completes the digestion in thirty minutes (±one minute). The result may then be conveniently expressed by dividing the weight of starch

[1] Two grams of iodin and 4 grams of potassium iodide are dissolved in 250 mils water. For use, 2 mils of this solution are diluted to 1 liter and 5 mils of this dilute solution are employed for each test.

(2.5 grams) by the weight of enzyme required to digest it under these fixed conditions.

U. S. P. Method for Assaying Diastase.—Mix a quantity of potato starch, purified as directed under Pancreatin, equivalent to 5 grams of dry starch, in a beaker with 10 mils of cold distilled water. Add 140 mils of boiling distilled water, and heat the mixture on a water-bath with constant stirring for two minutes, or until a translucent, uniform paste is obtained. Cool the paste to 40° C. in a water-bath previously adjusted to this temperature. Prepare a fresh solution of .1 gram of Diastase in 10 mils of distilled water at 40° C. and add it to the paste. Mix them well and maintain the same temperature for exactly thirty minutes, stirring frequently; a thin, nearly clear liquid is produced. Add at once .1 mil of this liquid to a previously made mixture of .2 mil of N/10 iodin V. S. and 60 mils of distilled water; no blue or reddish color is produced.

W. L. Baker's Method for Assaying Diastase.—A clean grade of potato starch is thoroughly washed and carefully dried at a low temperature and finally at a higher temperature to about a 10 per cent moisture content. The exact moisture content to be determined in a separate experiment. For the test enough of the starch is taken (about 11 grams) to make to 500 mils of an exactly 2 per cent (anhydrous) starch content. The boiling of the paste should be continued for ten minutes with constant stirring to keep from burning. For each test quantities of exactly 25 grams of the paste are weighed in a series of 250-mil flasks placed in a water-bath and kept at a temperature of 40° C. The iodin test solution is made by dissolving 2 grams of iodin and 4 grams of potassium iodide in 250 mils of distilled water, 2 mils of this solution is then diluted with pure water to make 1000 mils. The diastase solution is made by dissolving or suspending .2 gram of diastase in 100 mils of distilled water. The solutions are used in the following way: Definite volumes of the solution are added to the different flasks containing the starch solution and the mixtures are well shaken. The volumes added may be as follows: 4 mils, 4.5 mils, 5 mils, 5.5 mils, 6 mils. In eight minutes tests are begun by removing volumes of 5 drops from each of the digesting mixtures by a pipette, and adding this to 5 mils of the dilute iodin solution in a clear white tube standing over white paper. If at the end of ten minutes drops from one of the flasks fail to give the iodin reaction, we are ready for the more accurate test; for example, the flasks containing 5 mils diastase solution did not respond to the iodin reaction, but the one containing 4.5 mils did, then a second test should be carried out under exactly the same conditions as the former, using 4.6, 4.7, 4.8, 4.9, and 5 mils diastase solution to 25 grams of the starch paste. The diastase solution must be of the same temperature as the starch paste. The test is carried to the loss of all color. The diastase solution should have been just previously made

and, if working for any length of time, fresh solutions should be made from time to time, as aqueous solutions of diastase are very unstable and soon lose their power of conversion. The dilute iodin solution should not be put in the tubes until just before it is needed.

The method of Johnson used for determining the amylolytic value of pancreatin is applicable to diastase and malt preparations.

Malt Extract

Malt extract is prepared by extracting ground malt with water and concentrating to the consistency of molasses. It is a viscid liquid containing from 45 to 55 per cent of maltose, protein, water, ash, and diastase. When ready for market it is often treated with 8 to 15 per cent of alcohol. Malt extract is often combined with other remedial agents, cod liver oil, Cascara sagrada, digestives, hypophosphites, creosote, ferric pyrophosphate, quinin, strychnin, Yerba santa, etc.

Malt preparations are assayed for digestive power in the same way as diastase.

As remedial agents malt preparations are used almost exclusively for their amylolytic value. Malt, however, appears to contain ferments possessing proteolytic activity, and attention must be directed to the work on this subject which has been conducted by Wahl [1] and the procedure adopted by him in measuring this activity.

A mixture of preferably about one part of crushed malt and four parts of water, inoculated with lactic acid ferment, was subjected to a temperature varying between 50 and 60° C. maintained for about thirty minutes to destroy all organisms except the one to be propagated for producing the desired acid, and holding the temperature of the mash at 50° to 55° C. for about twenty-four to fourty-eight hours, during which time from 1 to 2 per cent of lactic acid is formed. The grains are then separated from the liquid, and same is used for the malt extractions made as follows:

One part, either of finely ground malt (Seck mill set at 1.0) or of coarsely ground or crushed malt (Seck mill set at .5), is extracted with four parts of the bacterial liquor above mentioned, previously diluted with water so as to give the desired strength of 105 per cent acidity. Varying temperatures were used for the extractions as specified below.

The peptic strength of the malt extracts was determined by autodigestion and by means of a modified "gelatin liquefying strength" method of Schidrowitch. In every instance the peptic strength of the malt extract was compared with that of a standard solution of pepsin of known strength. The method of conducting the test, as well as the preparation of the pepsin standard, are given below.

[1] 8th International Congress of Applied Chemistry, XIV, 221.

Preparation of the Gelatin.—Thirty-two grams of the gelatin are dissolved in 318 mils of distilled water by gently heating the same. One-third of a gram of finely ground egg albumen dissolved in 50 mils of distilled water is then added and the gelatin solution cooled to 52° C. The temperature is then raised to 85 ° C. in five minutes, and then to 100° C. where it is held for ten minutes. While still hot the gelatin is filtered into a glass beaker containing .5 gram of thymol, which readily dissolves in the liquefied gelatin. The solution is then tubed, each tube receiving 6 mils and the tubes closed with cork stoppers to prevent evaporation.

Method of Work.—(Testing of proteolytic strength.) The gelatin tube is gently warmed, preferably in a thermostat or water-bath, until the contents are liquefied. Five mils of the liquid under examination are then added to the tube. A blank is prepared at the same time, containing 5 mils distilled water. The tubes are then placed in an incubator held at 37.5° C. and incubated for four hours. After this they are placed in ice water at 2° C. and the time required for solidification of gelatin is noted. From the number of minutes required by the tube containing the liquid under examination, the time required for the solidification of the blank is subtracted, and the results tabulated for purposes of comparison. It must be remembered that a malt extract in which the enzyme has been destroyed, and which contains from 1 per cent to 2 per cent of lactic acid, has a slight power to liquefy gelatin, to the extent of requiring from one to two minutes longer to solidify than the blank.

Pepsin Standard.—.15 gram of pepsin of 10,000 strength is mixed with 10 grams of powdered sugar, and dissolved in 100 grams of distilled water. Five mils of this solution are added to a gelatin tube. The contents of a tube so prepared requires seven minutes for solidification.

The amount of *coagulable albumen* remaining in the malt extracts after the same had been subjected to the action of the peptonizing enzyme for a given period and at a given temperature was determined by means of the *coagulation test* conducted in the following manner:

The extract was filtered perfectly clear and then heated to 75° C., where it was held for thirty minutes and then allowed to cool to 25° C. Ten mils of this solution were introduced into a centrifuge tube graduated in 1/10 mils. The tube was placed in the centrifuge and run for a period of four minutes, at a speed of about 2500 revolutions per minute. The amount of coagulable albumen in the tube is then read in terms of 1/10 mil.

CHAPTER XXIV

OILS

The chemist is often confronted with the problem of determining the identity of an oil, or knowing its identity to determine its purity; he may be required to determine the kind and amount of an oil in a mixture of which a certain oil is one of the constituents; he may have to know the different kinds of oils and the approximate proportion of each in a mixture of oils; and finally it may develop that it is essential to determine the identity of an oil used in the preparation of soaps or the salts of the higher acids used as the basis of plasters and complex ointments.

The characteristics of the individual fixed and volatile oils and fats are described in great detail in works devoted to this subject, and it is not the province of this work to go into a detailed account of all of them. But there are a few oils which are used extensively as remedial agents or as the components of pharmaceutical preparations to which attention must be directed. Of the fixed oils, castor, olive, cod-liver, chaulmoogra, croton, theobroma, linseed, and mineral oils are used therapeutically. and in addition to these cotton-seed, sesame, sweet almond, arachis (peanut) enter into the composition of pharmaceutical mixtures, while the solid fatty substances, petrolatum, lard, tallow, and palm oil have also an extended use. The most important volatile oils encountered by the drug chemist include those of bitter-almond, anise, betula, gaultheria, cajuput, chenopodium, copaiba, cinnamon, cloves, eucalyptus, penny-royal, juniper berry, peppermint, pinus pumilio, santalwood, sassafras, savine, tansy, and turpentine.

The chemical characteristics, as well as the therapeutic value of some of these oils, are dependent on certain well-defined chemical individuals, of which often the pure oil is entirely composed, and their consideration is best effected among the systematic groups of chemical individuals to which the individuals belong.

General Methods for Examination.—*Specific Gravity.*—To be determined with pycnometer or Westphal balance.

Refractive Index.—To be obtained with a refractometer.

Acid Value.—Use 20 grams of fat or oil and 50 mils 95 per cent alcohol. Titration figure obtained can be used for calculating free fatty acid as

oleic. One mil N/10 alkali = .0282 gram oleic acid. One mil N/2 alkali = .1410 gram oleic acid.

Saponification Value.—The saponification value of a fat or oil is the quantity of potassium hydroxide (expressed in milligrams) consumed in saponifying 1 gram of the fat or oil. It is determined as follows: Weigh accurately, in a flask of 200 to 250 mils' capacity, 1.5 to 2 grams of the filtered fat or oil and add to it 25 mils of alcoholic potassium hydroxide accurately measured from a burette or pipette. Insert into the neck of the flask, by means of a perforated stopper, a glass tube from 70 to 80 cm. in length and from 5 to 8 mm. in diameter and heat the flask on a water-bath for half an hour, frequently imparting a rotatory motion to the contents. Then add 1 mil of phenolphthalein and titrate the excess of potassium hydroxide with half-normal hydrochloric acid. Make a blank test at the same time, using exactly the same amount of alcoholic potassium hydroxide. The difference in the number of mils of half-normal hydrochloric acid consumed in the actual test and the blank, multiplied by 28.055 and divided by the weight of the fat or oil taken, gives the saponification value.

Iodin Number.—The iodin value or number of a fat or oil indicates the proportion of iodin absorbed under specified conditions. It is determined as follows: Introduce about .8 gram of a solid fat or about .3 gram [1] of an oil, accurately weighed, into a glass-stoppered bottle of 250 mils capacity, dissolve it in 10 mils of chloroform, add 25 mils of iodo-bromide accurately measured from a burette or pipette, stopper the bottle securely, and allow the mixture to stand for half an hour [2] in a cool place protected from light. After this time it must still retain a brown color; if the color is not brown a new test should be started, using smaller a quantity of the fat or oil. Then add in the order named 30 mils of potassium iodide, 100 mils of distilled water, and N/10 sodium thiosulphate in small, successive portions, shaking thoroughly after each addition, until the color of the mixture becomes quite pale. Then add a few drops of starch and continue the addition of N/10 sodium thiosulphate until the blue color is discharged. While this test is being carried out, make a blank test by mixing exactly the same quantities of iodo-bromide and chloroform and titrating the free iodin with N/10 sodium thiosulphate as directed above. The difference in the number of mils of N/10 sodium thiosulphate consumed by the blank test and the actual test, multiplied by 1.269 and divided by the weight of the fat or oil taken, gives the iodin value.

Unsaponifiable Matter.—Weigh from 5 to 10 grams of the oil or fat into a 300-mil Erlenmeyer flask, add 100 mils of alcoholic potash (40

[1] .15 to .18 gram for linseed oil, .18 to .2 gram for cod liver oil, and .8 to 1.0 gram for oil of theobroma.

[2] One hour is required for castor oil and linseed oil.

grams per liter) and heat on the water-bath until saponification is complete. A small funnel in the neck of the flask will serve as a reflux condenser. After saponification, which usually takes from thirty to forty-five minutes, the hot soap solution [1] is poured into a 16-oz. Squibb separator and the flask rinsed with two 25-mil portions of 95 per cent alcohol, making a total of 150 mils of 95° alcohol. The separator is cooled to room temperature by shaking under the tap and 75 mils of light petroleum ether boiling below 80° added. The petroleum ether dissolves in the alcohol, forming a clear solution.

About 125 mils of water are next added and the mixture shaken. At this point the petroleum ether will separate and rise to the surface of the alcohol-water mixture in a clear layer. The soap solution is drawn off into a second separator and extracted twice with 50-mil portions of petroleum ether. The combined petroleum ether extracts are filtered into a tared beaker and evaporated on the water-bath. The residue is dried in a vacuum desiccator and weighed.

SPECIAL TESTS

Cottonseed Oil

Halphen Test.—Mix carbon disulphide, containing about 1 per cent of sulphur in solution, with an equal volume of amyl alcohol. Mix equal volumes of this reagent and the oil under examination, and heat in a bath of boiling, saturated brine for one to two hours. In the presence of as little as 1 per cent of cottonseed oil, a characteristic red or orange-red color is produced.

Lard and lard oil from animals fed on cottonseed meal will give a faint reaction; their fatty acids also give this reaction.

The depth of color is proportional, to a certain extent, to the amount of oil present, and by making comparative tests with cottonseed oil some idea as to the amount present can be obtained. Different oils react with different intensities, and oils which have been heated from 200–210° C. react with greatly diminished intensity. Heating ten minutes at 250° C. renders cottonseed oil incapable of giving the reaction.

Peanut Oil

Weigh 20 grams of the oil into an Erlenmeyer flask. Saponify with alcoholic potash solution, neutralize exactly with dilute acetic acid, using

[1] The alcohol content of the soap solution after dilution with water should be very close to 55 per cent by volume. It is necessary to know the volume of the alcoholic potash solution as well as the amount of alcohol used in rinsing the flask. A lower content of alcohol than 50 per cent will result in emulsions, while a higher percentage than 60 will cause the retention of a large part of the petroleum ether in solution.

phenolphthalein as an indicator, and wash into an 800- to 1000-mil flask containing a boiling mixture of 100 mils of water and 120 mils of 20 per cent lead acetate solution. Boil for a minute and then cool the precipitated soap by immersing the flask in water, occasionally giving it a whirling motion to cause the soap to stick to the sides of the flask. After the flask has cooled, decant the water and excess of lead acetate solution and wash the lead soap with cold water and 90 per cent alcohol by volume. Add 200 mils of ether, cork and allow to stand for some time until the soap is disintegrated; heat on a water-bath, using a reflux condenser, and boil for about five minutes. In the case of oils, most of the soap will be dissolved, while in lards, which contain much stearin, part of the soap will be left undissolved. Cool the ether solution of soap to 15–17° C. and allow to stand until all the insoluble soaps have separated out (about twelve hours).

Filter upon a Buchner funnel and thoroughly wash the insoluble lead soaps with ether. Wash the ether-insoluble lead soaps into a separatory funnel by means of a jet of ether, alternating at the end of the operation, if a little of the soap sticks to the paper, with hydrochloric acid (1 to 3). Add sufficient hydrochloric acid (1 to 3) so that the total volume of the latter amounts to about 200 mils and enough ether to make the total volume of it 150–200 mils and shake vigorously for several minutes. Allow the layers to separate, run off the acid layer, and wash the ether once with 100 mils of dilute hydrochloric acid, and then with several portions of water until the water washings are no longer acid to methyl orange. If a few undecomposed lumps of lead soap remain (indicated by solid particles remaining after the third washing with water), break these up by running off almost all the water layer and then add a little concentrated hydrochloric acid, shake, and then continue the washing with water as before. Distill the ether from the solution of insoluble fatty acids and dry the latter in the flask by adding a little absolute alcohol and evaporating on a steam-bath. Dissolve the dry fatty acids by warming with 100 mils of 90 per cent alcohol by volume and cool slowly to 15° C., shaking to aid crystallization. Allow to stand at 15° C. for thirty minutes. In the presence of peanut oil, crystals of arachidic acid will separate from the solution. Filter, wash the precipitate twice with 10 mils of 90 per cent alcohol by volume, and then with 70 per cent alcohol by volume, care being taken to maintain the arachidic acid and the wash solutions at a definite temperature in order to apply the solubility corrections given below. Dissolve the arachidic acid upon the filter with boiling absolute alcohol, evaporate to dryness in a weighed dish, dry, and weigh. Add to the weight .0025 gram for each 10 mils of 90 per cent alcohol used in the crystallization and washing, if conducted at 15° C.; if conducted at 20° C., add .0045 gram for each 10 mils. The melting-point of arachidic acid

thus obtained is 71 to 72° C. Twenty times the weight of arachidic acid will give the approximate amount of peanut oil present. Arachidic acid has a characteristic appearance and may be identified by the microscope. As little as 5 to 10 per cent of peanut oil can be detected by this method.

Sesame Oil

Baudoin Test.—Dissolve .1 gram of finely powdered sugar in 10 mils of hydrochloric acid (sp. gr. 1.20), add 20 mils of the oil to be tested, shake thoroughly for a minute and allow to stand. The aqueous solution separates almost at once and, in the presence of even a very small admixture of sesame oil, is colored crimson. Some olive oils give a slight pink coloration with this reagent. Comparative tests with known samples containing sesame oil will differentiate them.

Villavecchia Test.—Add 2 grams of furfural to 100 mils of 95 per cent alcohol by volume and mix thoroughly .1 mil of this solution, 10 mils of hydrochloric acid (sp. gr. 1.20), and 10 mils of the oil by shaking them together in a test-tube. A crimson color is developed as in the Baudoin test, where sugar is used.

Villavecchia explained this reaction on the basis that furfural is formed by the action of levulose and hydrochloric acid and therefore substituted furfural for sucrose. As furfural gives a violet tint with hydrochloric acid it is necessary to use the very dilute solution specified in the method.

Cholesterol and Phytosterol

Introduce 200 to 300 grams of the melted fat into a flat-bottomed liter flask. Close the neck of the flask with a three-holed stopper and insert through these holes: (1) a reflux condenser; (2) a right-angled glass tube, one arm of which reaches to a point 6 mm. above the surface of the melted fat, the other being closed a short distance from the flask by means of a short piece of rubber tubing and a pinch-cock; (3) a glass tube bent so that one arm reaches down to the bottom of the flask and the other serves as a delivery tube for a 700-mil round-bottomed flask containing 500 mils of 95 per cent alcohol by volume.

Place the flasks containing the melted fat and the alcohol on a steam-bath and heat so that the alcohol vapor passes through the melted fat in the liter flask and is condensed in the reflux condenser, finally collecting in a layer over the melted fat. After all the alcohol has passed in this manner into the flask containing the fat, disconnect the flask from which the alcohol has been distilled and attach a tube to the short piece of rubber tubing attached to the right-angled glass tube (see (2) above) and siphon the alcohol layer back into the alcohol distillation flask. Reconnect as at first and again distill the alcohol as in the first operation. When all

the alcohol has been distilled, siphon it again into the distillation flask and extract in the same manner for a third time.

Discard the fat and retain the alcohol, which now contains practically all of the cholesterol and phytosterol originally present in the fat. Concentrate the alcoholic solution to about 250 mils and add 20 mils of potassium hydroxide solution (1 to 1) to the boiling liquid. Boil for ten minutes to insure complete saponification of the fat, cool to room temperature and pour into a large separatory funnel containing 500 mils of warm ether. Shake to insure thorough mixing and add 500 mils of water. Rotate the funnel gently to avoid the formation of extremely stubborn emulsions, but mix the water thoroughly with the alcohol-ether-soap solution. A clear, sharp separation takes place at once. Draw off the soap solution the wash the ether layer with 300 mils of water, avoiding shaking. Repeat the washing of the ether solution with small quantities of water until all the soap is removed. Transfer the ether layer to a flask and distill the ether until the volume of liquid remaining in the flask measures about 25 mils. Transfer this residue to a tall 50-mil beaker and continue the evaporation until all the ether is driven off and the residue is perfectly dry. If desired a tared beaker may be used and the weight of the unsaponifiable matter determined at this point.

Add 3 to 5 mils of acetic anhydride to the residue in the beaker, cover the beaker with a watch-glass and heat to boiling over a free flame. After boiling for a few seconds, remove the beaker from the flame, cool and add 35 mils of 60 per cent alcohol by volume. Mix the contents of the beaker thoroughly, filter off the alcoholic solution, and wash the precipitates with 60 per cent alcohol. Dissolve the precipitate on the filter with a stream of hot 80 per cent alcohol by volume and wash the insoluble portion well with 80 per cent alcohol. Acetates of cholesterol and phytosterol are dissolved while the greater portion of the impurities present (including paraffin and paraffin oil if present) remain behind on the filter. Cool the combined filtrate and washings to a temperature of 10–12° C. and allow to stand at that temperature for two to three hours. During this time the acetates of cholesterol and phytosterol crystallize from the solution. Collect the crystals upon a filter, wash with cold 80 per cent alcohol and then dissolve them in a minimum amount of hot absolute alcohol. Collect the alcoholic solution of the acetates in a small glass evaporating dish, add 2 or 3 drops of water to the solution and heat if not perfectly clear. Allow the alcohol to evaporate spontaneously, the contents of the dish being stirred occasionally to mix the deposit of crystals which form upon the edges with the main body of the liquid. As soon as a good deposit of crystals has formed, collect them upon a hardened filter, wash twice with cold 80 per cent alcohol, and dry by suction, drying finally at 100° C. for thirty minutes, and determine the melting-point.

The melting-point of the first crop of crystals usually gives definite information as to the presence or absence of phytosterol, but the conclusion indicated should be confirmed by recrystallizing the crystals from absolute alcohol and again determining the melting-point. If the crystals are pure cholesteryl acetate, the melting-point of the second crop should agree closely with that of the first. If phytosteryl acetate is present, however, a higher melting-point will be noted, as phytosteryl acetate is less soluble in alcohol than cholesteryl acetate. The melting-point of cholesteryl acetate is 114° C., that of phytosteryl acetate 125–127° C.

SUMMARY OF CONSTANTS OF MOST IMPORTANT FIXED OILS USED IN MEDICINES

Oil	Sp. Gr. at 25°	Sapon. Value	Iodin Value	Rotation
Castor	.945 –.965	179–185	83–88	+23.4°–+26.1°
Olive	.910 –.915	190–195	79– 90	
Cod Liver	.9196–.922	180–190	150–170	
Croton	.935 –.950	200–215	104–110	Strongly dexto
Chaulmoogra (true oil)	.951	213	103	$(\alpha)_D$ +52°
Gynocardia Oil (false Chaulmoogra)	.925	197	152	
Theobroma	.973	188–195	33– 38	
Linseed	.925 –.930	187–195	170	
Cotton Seed	.915 –.921	190–198	105–114	
Sesame	.916 –.921	188–193	103–112	
Sweet Almond	.910 –.915	191–200	93–100	
Peanut	.911 –.926 at 15°	186–194	83–101	

Cod-liver Oil

The oil expressed from the livers of the cod is the most extensively used medicinal oil. It is dispensed in the free state and as an emulsion, and in the latter form is often combined with sodium and calcium hypophosphites, creosote, wine, and phosphoric acid. In soluble elastic capsules it is combined with phosphorus, creosote, and iodoform. The emulsions of the oil are not to be confused with the preparations containing cod-liver extract. The latter is really a mixture of proteins, animal acids and salts obtained by extracting the livers with an alcoholic menstruum, and little or no actual oil is present. This cod-liver extract is combined with iron and manganese peptonates, hypophosphites, strychnin, bile acids, wine, and flavoring agents. The combinations are sold under various trade names, and the labels and literature usually contain some reference to the presence of the cod-liver principles.

The composition of cod-liver oil has been surrounded with more or less

mystery, and its virtues have been attributed to many causes, such as nitrogenous or alkaloidal constituents, the presence of organic iodin or of organic phosphorous, the absence of hydroxyl glycerides, etc., and it is of interest to present a few facts concerning the actual composition of a pure medicinal oil.

The limits of specific gravity for a high-grade cod-liver oil are about .9196 to .922 at 25°; the iodin value averages between 150 and 170, with a few oils going above or below these figures; the index of refraction runs from 1.4783 to about 1.4822; the saponification value is from 180 to 190; and a pure oil does not congeal above −.11° C. In connection with the saponification value it should be stated that the determination is of little moment except in cases of very light oils. With dark oils the end-point becomes so obscured that accurate titration is impossible.

In one of the color tests recommended for cod-liver oil, 20 drops of the oil are placed in a watch-glass over white paper and treated with one to two drops of concentrated sulphuric acid, carefully added to avoid mixing, then the acid and oil intimately stirred, and the color change noted. When stirred, pure light-colored oils give a play of colors: at first purplish red, changing quickly to a ruby red, then a deep mahogany color and more slowly to a warm brown; around the edge, the thin layer of liquid assumes a pale-blue tinge, and on standing from one-half to one hour a purple shade develops, the mixture becoming dark brown on long standing. Some oils, especially the darker colored, pass directly to the mahogany and dark-brown stage without showing the reds, and become almost black on standing, with little or none of the purplish ring around the edge. Cusk and pollock liver oils, even after four years' standing, give the same play of colors as genuine cod-liver oil. This test may be varied by dissolving the oil in carbon bisulphide or chloroform and adding sulphuric acid; but the same general results are obtained, though the shades of color are perhaps slightly different.

The test with fuming nitric acid, described in the Pharmacopœia, gives varying results. Some samples of known purity do not become rose red, but turn purple or brownish and then change to brick red. The description of this test is incomplete, as the color is first pale rose, which soon gives way to a brick red and very gradually changes to yellow. In some cases, also, the brick-red color does not change to yellow, but to a brown; and in others again it does not fade to a purple yellow at all, but remains reddish.

In connection with the actual composition of cod-liver oil, attention must first be called to some work performed in 1890 by Gautier and Morgues, and in 1906 by Bull. The investigations of the former were concerned with the nitrogenous constituents of cod-liver oils, and of the latter with the actual composition of a pure oil.

Gautier and Morgues found that the dark-colored oils, which, by the way, are never used medicinally and are really extracted from livers that are partially putrefied, contain the following well-defined nitrogenous bases: butylamine, amylamine, hexylamine, dehydrolutidine, aselline, and morrhurine. With the exception of the two latter, these bases have been known for some time, and no special virtue is attributed to them. Bull,[1] working with pure oils free from nitrogen, endeavored to identify the acids which made up the glycerides. He converted the mixed acids into their methyl esters, fractionated them, and separated the following acids: oleic, myristic, palmitic, erucic, gadolinic, and a new acid.

The work done by Tolman and myself at the Bureau of Chemistry fully verified the conclusions of these workers and showed that a high-grade oil contained no nitrogenous constituents nor any iodin or phosphorus compounds, but was a mixture of neutral glycerides, and that its good effects are probably attributable to its being a ready assimilable fat.

The figures given in the 9th revision of the U. S. P. as applying to a cod-liver oil of standard purity are nearly all incorrect, and the test for the limit of free fatty acids is vague and of no value. Oils of high purity will often contain nearly 1 per cent of free acid. The figures and the color tests together are not limited to cod-liver oil, but will apply equally well to carefully refined oils from other fish livers; though it should be stated that in this investigation the oils from the livers of American cod and other American fish lose their original character and become unfit for medicinal use after three to four years.

The fact that highly refined liver oils show practically the same constants and answer the same tests is of interest to those who are engaged in the oil business, as it shows the possibilities of a new industry for utilizing oils of hitherto valueless livers, not for the purpose of adulterating cod-liver oils but for their own value as medicinal agents.

It will be noted that the determination of the identity of a fish oil is not a matter of absolute certainty. The most rational method would be the conversion of the glycerides to the methyl esters of the acids and identifying the components of the mixture, which is a long and tedious operation and almost impossible of attainment unless the sample is of sufficient bulk. Another complication arises from the fact that the composition of the glycerides of oils other than cod-liver oil has never been determined. Hence it appears that about all an analyst is justified in saying is that the oil is a fish oil and perhaps a fish liver oil.

If it is desired to determine the quantity of oil in a capsule, a funnel with a wide bowl should be placed so that it can drain into a graduated cylinder and 5 to 10 capsules slit with a knife, dropped into the bowl of the funnel and the contents allowed to drain into the graduate.

[1] Berichte, 1906, 39, 3570.

Emulsions are examined for their content of oil by transferring a measured quantity to a separatory funnel, adding water if very thick and then a quantity of alcohol until the emulsion breaks. This procedure does not always suffice, and it may be necessary to warm the diluted emulsion by rotating the containing vessel over the steam-bath, or to cool in a freezing mixture, or to add lead acetate. After the emulsion breaks up the oil can be shaken out with petroleum ether or ether using two or three portions and the combined solvent mixtures filtered through a dry filter and evaporated over the steam-bath. The residue is then measured or weighed and the figure may be used for obtaining a fairly close approximation of the quantity present in the emulsion. With substances of this nature it is difficult to obtain results of great accuracy, because the oil gains weight when heated and it is difficult to remove the last traces of the solvent.

Castor Oil

Castor oil, which is expressed from the seeds of Ricinus communis (Euphorbiaceæ) is a popular laxative remedy. It is usually dispensed in capsules and is sometimes combined with Podophyllum resin. The capsules of Aspidium (Malefern) used for the expulsion of tape worm contain castor oil. It is combined with croton oil in veterinary remedies.

Castor oil is the only commonly occurring non-volatile expressed oil which is readily soluble in 95 per cent alcohol and in 5 parts 90 per cent alcohol, and this simple test is sufficient to indicate the identity of a sample under examination. It also deviates the plane of polarized light to the right unless it has been heated to 270° C. It is composed chiefly of the glyceride of ricinolic acid.

Castor-oil mixture is an emulsified preparation of the oil with acacia flavored with cinnamon and orange flower water.

Castor oil is incorporated with magnesium oxide and sold as dry powder.

Olive Oil

The use of this oil as an internal lubricant and a nutritive agent is on the increase. It is prepared in enormous quantities and marketed in a state of great purity. Besides being sold by itself as a medicinal agent, it is combined with other drugs to furnish a bland medium for administration and the additional therapeutic action. It will be found combined with apiol; Cascara sagrada extract; copaiba; pennyroyal oil; creosote; oleoresin malefern and kamala, oleoresin saw palmetto; salol, cubeb oleoresin; santal oil and pepsin, etc.

Sweet Almond, Peach, and Apricot Kernel Oils

These three oils resemble each other closely in appearance and properties, and may be and probably often are substituted for each other. For all practical purposes their properties are identical, and are closely allied to olive and other bland fixed oils like cottonseed and sesame.

Most of these bland oils which are now obtainable in a state of great purity are used as vehicles and for their lubricating and emollient value in inhalants and embrocations.

In the early days of the administration of the Food and Drugs Act, the importation of these three oils was the subject of considerable scrutiny, and their absolute differentitation was found to be a matter of difficulty. The practice of mixing one with another was evidently in vogue, and the actual determination of the composition of such a product was practically impossible. As with other oils, the only feasible way of showing any difference between them would be to determine the character of the mixed glycerides, and to apply the knowledge gained in examining the suspected samples. At present the dependence on the difference in color reactions given with certain reagents is too uncertain to be used as a final criterion of differentiation. The improvements in the methods of refining oils have advanced to such a degree that it is possible to eliminate many of the impurities to which the color tests were probably attributable. Again the study of oils has developed the possibilities of manipulation, and by simple treatments it is often easy to render an oil incapable of yielding some of the simple tests which a few years ago were sufficient for its identification.

Expressed oil of almond is the base of phosphorated oil.

Croton Oil

Croton oil from the seeds of Croton tiglum is a component of hepatic stimulants and purgative mixtures. On account of its drastic action it is not dispensed by itself, but is combined in small quantity with other laxative and stimulant drugs which are prepared for use in the form of pills and tablets. The combinations are generally of the following types aloes, gamboge, Podophyllum resin, Capsicum and croton oil; aloin, Nux Vomica, Podophyllum resin, gamboge, Veronica virginica, Capsicum, Veratrum viride, calomel and croton oil; Aloes, scammony, myrrh, caraway oil, mercury mass, and croton oil. It is also present in some of the liquid cathartic mixtures combined with Cascara sagrada. It is sometimes employed externally in cases where a strong counter-irritant is desired, and in veterinary practice has proven a valuable remedy for lump jaw.

Compte [1] recommends the following identification test: When the pure oil or a mixture with other oils is shaken with twice its volume of absolute alcohol, the clear alcholic liquid poured into a highly concentrated solution of sodium potassium hydroxide and the mixture warmed thirty seconds in a boiling water-bath and allowed to stand, an intense reddish-brown or reddish-violet ring forms at the junction of the liquid.

If during the analysis of a laxative mixture, an oily substance is separated, a few drops rubbed on the under side of the forearm will cause a characteristic eruption if it is croton oil.

Cottonseed Oil

This oil is obtainable in a high degree of purity, and is being recommended as a nutritive, for which purpose it is expected to rival olive oil. It is used as a vehicle for camphor, menthol, and other medicinal agents, and adds to their virtues the additional value of a lubricant in case of sprains and stiffness of the joints.

Sesame Oil

Sesame oil is employed as a vehicle and a lubricant, and is one of the components of some of the oily preparations extensively advertised for their value as local applications to the mammary and external genital organs and the abdomens of pregnant women.

A characteristic test for this oil and which is useful in detecting it in admixture with other oils is obtained by shaking 1 mil with 1 mil of concentrated hydrochloric acid containing 1 gram of cane sugar, when a rose-red color develops in fifteen minutes, changing gradually to violet. With other fixed oils no coloration develops for nearly an hour.

Chaulmoogra Oil

This oil has powerful alterative properties, and is used as a remedy for leprosy. Its source was for a time uncertain, but it is now known that the true oil is expressed from the seeds of Taraktogenos kurzii King. Several species of Hydnocarpus, as H. venenata, H. wightiana, and H. anthelmintica, yield oils of similar chemical composition, the oil from the former being known as false chaulmoogra.

The oil from Gynocardia odorata, which was considered at one time the source of chaulmoogra, has an entirely different make-up. It is also a liquid, while the true oil is a soft solid below 22°.

[1] J. Pharm. Chim., 1916, 14, 38.

Chaulmoogra oil is optically active and consists to a large extent of the glyceryl esters of optically active cyclic acids of the general formula, $C_nH_{2n-4}O_2$. Power,[1] who isolated these acids, designated that present in largest amount chaulmoogric acid, $C_{18}H_{32}O_2$. This acid melts 68° with $(\alpha)_D 56°$. A small amount of palmitic acid and a phytosterol are present.

Gynocardia oil is optically inactive and contains none of the members of the chaulmoogric acid series. It consists of glycerides of linolic acid or isomerides of the same series, palmitic, linolenic, and isolinolenic acids, and a phytosterol, melting 133°. The seeds of Gynocardia contain a cyanogenetic glucoside, gynocardin.

True chaulmoogra oil has a high acid value 23–24, while the false oil is low, 4–5.

Oil of Theobroma. Cocoa Butter

This oil solidifies below 30° C. and has a characteristic odor. It is extensively employed as a suppository base and functionates to a slight extent in the composition of ointments and salves.

VOLATILE OILS

General Methods for Examination.—*Specific Gravity.*—To be determined with pycnometer or Westphal balance.

Optical Rotation.—To be determined with a polarimeter or saccharimeter. Polarimeters permit the angle of rotation to be read off in degrees or fractions of a degree of a circle. Saccharimeters set to measure percentage of sucrose, give readings in terms of divisions of the sugar scale.

One division Laurent sugar scale equals .2167° angular rotation D.

One division Schmidt & Hansch sugar scale equals .346° angular rotation D.

Specific Rotatory Powder.—The rotatory power of an optically active, liquid substance, observed with sodium light, and referred to the ideal density 1, and in the tube having the length of 1 decimeter (100 mm.)., is designated as its specific rotatory power. This is usually expressed by the term $(\alpha)_D$. Since, however, not only the density of an optically active liquid, but also its rotation, is influenced by the temperature, the specific rotation varies with the latter. In stating the specific rotation it is, therefore, necessary to indicate at what temperature the rotation and the density of the liquid have been determined. But for the same

[1] Amer. J. Pharm., 87, 1915, 493.

temperature the specific rotation of a pure, optically active liquid is always a constant number. The temperature used in the text of the Pharmacopœia is 25° C., except when otherwise indicated. For saccharimeters the temperature is fixed at 20° C. by international agreement.

For calculating the specific rotatory power of an optically active liquid substance, or solution of an optically active solid, the following formulas are of general application:

I. For liquid subtances $(\alpha)_D = \frac{100 \times a}{L \times d}$

II. For solutions of solids $(\alpha)_D = \frac{10000 \times a}{L \times p \times d}$

or

$$(\alpha)_D = \frac{10000 \times a}{L \times c}$$

For calculating these formulas the determination of the following factors is necessary:

a = the angle of rotation of the liquid or solid observed with sodium light;

L = the length of the tube in millimeters;

d = the density of the active liquid or solution;

p = the amount of active substance in 100 parts by weight of the solution;

c = the number of grams of active substance in 100 mils of solution.

Solubility in alcohol of various strengths and in other solvents.

Saponification Value.—This is actually the sum of the acid and ester numbers. The former is the amount of KOH in milligrams necessary to neutralize the free acid in 1 gram of the oil. The latter is the amount used in the saponification of 1 gram.

The saponification is conducted in a wide-necked flask of potash glass of 100-mils capacity. A glass tube about 1 mm. in length and passing through a stopper serves as a reflux condenser. About 2 grams of oil are weighed accurately to 1 cg. into such a flask and 10 to 20 mils of the N/.5 alcoholic potash solution are added. Previous to this the oil should be tested for free acid, an alcoholic solution of phenolphthalein being used as indicator. The flask provided with the condensing tube is heated

for half an hour on a steam-bath, and after cooling, the contents are diluted with about 50 mils of water and the excess of alkali titrated back with half normal sulphuric acid.

Acetylization.—This is a measure of the alcohols of the Formulas $C_{10}H_{18}O$ and $C_{10}H_{20}O$.

For the quantitative acetylization 10 to 20 mils of the oil, mixed with an equal volume of acetic acid anhydride and 1 to 2 grams of dry sodium acetate, are boiled uniformly from one to two hours in a small flask provided with a condensing tube which is ground into the neck of the flask. After cooling, some water is added to the contents of the flask and then heated from one-quarter to one-half hour on a water-bath, to decompose the excess of acetic acid anhydride. The oil is then separated in a separating funnel, and washed with soda solution and water until the reaction is neutral. Of the acetylized oil dried with anhydrous sodium sulphate 2 grams are saponified according to the method described above. The amount of alcohol, based on the original unacetylized oil, corresponding to the saponification number, can be found by the formulas below.

For the calculation the following formulas may be used:

For the Alcohol, $C_{10}H_{18}O$

1. $\frac{196 \times \text{sapon. No.}}{56} = \text{per cent of ester}$
2. $\frac{154 \times \text{sapon. No.}}{56} = \text{per cent of alcohol}$
3. $\frac{a \times 15.4}{S - (a \times 0.042)} = \text{per cent of alcohol in original oil.}$

For the Alcohol, $C_{10}H_{20}O$

1. $\frac{198 \times \text{sapon. No.}}{56} = \text{per cent of ester}$
2. $\frac{156 \times \text{sapon. No.}}{56} = \text{per cent of alcohol}$
3. $\frac{a \times 15.6}{S - (a \times 0.042)} = \text{per cent of alcohol in original oil.}$

a = mils of normal KOH used.

S = grams of acetylated oil used for the saponification.

SUMMARY OF CONSTANTS OF THE MORE IMPORTANT VOLATILE OILS

Oil	Specific Gravity at 25° C.	Optical Rotation in 100-mm. tube
Bitter Almond	1.038–1.060	Inactive or not over +0° 10[1]
Anise	.978– .988	+10° to −2°
Star Anise	.980– .990	0° to −12°
Fennel	.953– .973	+12° to +24°
Caraway	.900– .910	+70° to +80°
Coriander	.863– .875	+ 8° to +13°
Sandalwood	.965– .980	−15° to −20°
Eucalyptus	Variable depending on species	Variable usually lævo
	.905–.925	
Orange	.842– .846	+91° to +98°
Cajuput	.912– .925	−4°
Clove	1.038–1.060	−1° 10′
Cassia	1.045–1.063	+1° to − 1°
Chenopodium	.955– .980	−4° to −10°
Cubeb	.905– .925	−20° to −40°
Juniper	.854– .879	0° to −15°
Lavender	.875– .888	−4° to −10°
Lemon	.851– .855	+57° to +64°
Peppermint	.896– .908	−23° to −35°
Spearmint	.917– .934	−38° to −55°
Nutmeg	.859– .924	+12° to +30°
Pimento	1.018–1.048	0° to −4°
Pine Needle (Pinus pumilio)	.853– .869	−3° to −10°
Rosemary	.894– .912	−9° to +18°
Sassafras	1.065–1.077	+3° to +4°
Mustard	1.013–1.020	Inactive
Turpentine	.860– .870	Variable
Thyme	.984– .930	Slightly lævo
Copaiba	See under drug	
Pennyroyal (American)	.920– .935	+18° to +22°
Pennyroyal (European	.930–.960 at 15° C.	+17° to +23°
Savin	.903– .923	+40° to +60°
Tansy	.925– .940	+30° to +45°

Oil of Bitter Almonds

The discussion of this oil will be found in the section devoted to Cyanogenetic Glucosides.

Oils of Anise and Star Anise

These oils are obtained from the fruits of plants belonging to entirely different families. The anise plant Pimpinella anisum belongs to the Umbelliferæ, while the species of Illicium which yield the star anise oil

belong to the Magnoliaceæ. Both oils contain anethol as their most important and valuable constituent, there is also a smaller quantity of the isomeric methyl chavicol. The two oils can be distinguished from each other only by odor and taste.

Anise oil is a colorless, highly refractive liquid which solidifies to a snow-white crystalline mass, melting 15–19° C. The solidification point of a sample of oil furnishes very good indication of the quality of the product, and may be determined as follows:

Transfer a small quantity of the oil to a test-tube and surround it with ice water or chipped ice, or a mixture of ice and salt. Insert a thermometer and allow it to remain undisturbed until the temperature has fallen to about 5° below the normal congealing point of the oil (in the case of star anise this is about 15° C. and the fennel about 3°). Then induce crystallization by stirring with the thermometer, removing the tube from the bath and continuing until solidification takes place. The highest temperature reached during the crystallization is regarded as the congealing point.

Anise oil has been reported adulterated with fennel oil, turpentine, cedar wood oil, copaiba, and gurjun balsam oil, alcohol, spermaceti, fixed oils. The presence of these adulterants is readily detected by a determination of the physical properties. Fennel oil and its stearoptene are the common adulterants, but they cause a dextro rotation and are easily detected. Pure anise oil undergoes oxidation if carelessly stored or exposed to the light, its specific gravity increases and its tendency to solidify disappears.

Star anise oil is a colorless or yellowish, highly refractive liquid, congealing between +14 and +18° C., and containing from 80–90 per cent of anethol with probably some methyl chavicol, and two terpenes, *d*-pinene and *l*-phellandrene, making up the balance.

This oil often replaces the oil from Pimpinella in medicinal preparations, but because of the amount in which it occurs and because of the modifying influence of the other constituents, no one could assert with any certainty as to the identity of the oil in any given mixture.

The chief use of these oils is for flavoring purposes, and as this characteristic is largely due to the anethol it matters little which one is present.

Fennel Oil

Fennel oils vary in their composition and consequently in their odor and flavor, but the ordinary oil of commerce contains from 50–60 per cent of anethol, fenchone, *d*-pinene, dipentene, and possibly other constituents. It is a colorless or slightly yellow liquid with a characteristic odor and taste, and solidification point of +3 to +6° C., rotation +12 to +24°. This oil comes from Lutzen, Roumania, Moravia, and Galicia.

Sweet or Roman fennel oil solidifies +10 to +12°, rotation +7 to +16°. Macedonian fennel oil solidifies +7 to +12°, rotation +5 to +12°. Both these oils contain no fenchone.

Indian fennel oil contains both anethol and fenchone, melting-point +8°, rotation +21°.

Japanese oil contains the characteristic constituents, solidifies +7°, rotation +10 to +16°.

Wild bitter fennel oil of France, Spain, and Algiers rotates +48° and consists principally of a terpene.

Caraway Oil

Caraway oil is a colorless, highly refractive liquid, becoming yellowish in time, with a characteristic odor and spicy taste. Its rotation is +70 to +80°. It is composed of carvone and *d*-limonene in about equal parts, and the carvone may be readily determined by the method described on page 607.

Coriander Oil

Oil of coriander is a colorless or slightly yellow liquid, rotating +8 to +13° and soluble in 3 parts of 70 per cent alcohol. It contains *d*-linalool (coriandrol) and about 5 per cent of *d*-pinene with other constituents to which the characteristic flavor is due. It is often adulterated with turpentine and orange oil, both of which modify the rotation and the rotatory power.

Sandal-wood Oil

There are several species of Santalum which yield oils, but the oil used for medicinal purposes is obtained from the wood of S. album, a medium-sized tree growing in India. The oil was formerly distilled in the East in large quantities, but owing to the fact that it was almost impossible to prevent adulteration, the users of the drug finally adopted the expedient of importing the wood and distilling their own oil. At the present time all pharmaceutical manufacturers of any pretensions have their own plants for distilling sandal-wood oil.

The oil is used principally for venereal diseases, and is dispensed in soluble elastic capsules either by itself or combined with copaiba oil or oleoresin cubeb, oleoresin matico, creosote, eucalyptol, salol, pepsin, oleoresin saw palmetto, methylene blue, or cinnamom oil. Pill and tablet formulas contain the same remedial agents, also ferrous sulphate, turpentine and methyl salicylate.

Oil sandal-wood or an extract is combined with saw palmetto and corn silk in elixirs of the sanmetto type.

The medicinal value of this drug is due to the santalol content, which according to our standard should be no lower than 90 per cent.

The santalol is determined in the same way that menthol is determined in peppermint oil, page 557. The formula for calculating the percentage follows:

$$\text{Per Cent} = \frac{A \times 11.11}{B - (A \times 0.021)}$$

A is the difference between the number of mils of N/2 sulphuric acid required in the titration and the number of mils of N/2 alcoholic potash originally taken; and B is the weight of acetylized oil taken.

Nelson [1] has described a procedure for the identification of some of the volatile oils more commonly occurring in medicinal preparations.

In case volatile oils are used merely as flavoring agents their identification is not so important, and they will be present in small quantity. But if used for their medicinal or antiseptic effect it will be desirable to obtain as large an amount as possible for the examination. A liberal sample of the preparation, neutralized if acid or alkaline, is submitted to steam distillation and the undissolved oily layer separated from the distillate.

The physical constants of the volatile oil mixture are first determined. The density is taken with a small Sprengel tube. The optical rotation and index of refraction are determined, and the boiling temperature is taken, keeping the fractions separate for each 10° difference and noting the amount and odor of each fraction. This will often afford a clue to the nature of the mixture and perhaps direct attention to some of the components.

Aldehydes (and some Ketones)

Separation.—The oil (or a suitable fraction) is shaken with an equal volume of a saturated solution of sodium hydrogen sulphite in a separatory funnel and allowed to stand with occasional shaking for from eight to twelve hours. If crystals separate they are filtered off; the aqueous layer is separated and the crystals added. To this solution add sufficient sodium carbonate to neutralize the acid sulphite, and distill with steam. Aldehydes will pass over into the distillate and will usually be recognized by their odor.

Benzaldehyde will indicate oil of bitter almonds; cinnamic aldehyde, oil of cassia; pulegone, oil of pennyroyal; methyl nonylketone, oil of rue; thujone, oils of tansy, wormwood, or sage. (The last three are ketones which react like aldehydes with sodium hydrogen sulphite.)

[1] J. Amer. Pharm. Assn., 6, 1917, 543.

Aldehydes: Identification

Benzaldehyde: Liquid, b.p. 733 mm. 177°; d. 15°/15°, 1.050–1.055; m.p. of semicarbazone, 214°; easily oxidized to benzoic acid.

Cinnamic aldehyde: Liquid, b.p. 252°; d_{15}°, 1.054–1.058; m.p. of semicarbazone, 208°; oxidized by cold potassium permanganate to benzaldehyde and benzoic acid.

Citral: Liquid with lemon-like odor; b.p., 228–229°; m.p. of citryl β-naphtho cinchoninic acid, 200°.

Aldehydes: Determination

Aldehydes and certain ketones (pulegone, carvone) can be estimated by the neutral sulphite method of Burgess.[1]

A saturated solution of sodium sulphite is prepared, and, if acid, is neutralized with a solution of sodium hydrate until a faint pink color is permanently maintained with phenolphthalein. To 50 mils of such solution 25 mils of the oil are added, and two drops of an alcoholic solution of phenolphthalein. The whole is then heated on a water-bath to nearly boiling-point, constantly shaking. A deep-red color almost at once appears, which shows that the action has commenced. A few drops of sulphurous acid are then cautiously added, and this is continued until no further color is produced after a further addition of SO_2. The oil is then measured. The obvious advantage of this method is that the end of the reaction may be ascertained to a certainty, while the above bisulphite method depends on the continual shaking for a period of not less than one hour.

Phenols: Separation

The oil left in the separatory funnel after treatment with sodium hydrogen sulphite, is shaken with two or three times its volume of a 5 per cent solution of potassium hydroxide. After the undissolved oil has separated the aqueous layer is filtered through a wet filter and a slight excess of dilute hydrochloric acid is added. A turbidity at this point will indicate the presence of phenols. Methyl salicylate separates with the phenols.

If the odor indicates the presence of methyl salicylate take up the separated phenols in a little ether; separate the ether solution and transfer it to a small flask; add from 5 to 10 mils of 5 per cent potassium hydroxide solution and warm on a water-bath under a reflux condenser to saponify the ester. Then pass in carbon dioxide to saturation and extract the

[1] J. Soc. Chem. Ind., 1901, 1179.

phenols (free from methyl salicylate) with ether. Acidify the aqueous solution and extract with ether; if methyl salicylate is present a residue of salicylic acid will be left on evaporating the ether, which can be identified by its melting-point and by the violet color its solutions give when treated with ferric chloride solution.

If methyl salicylate is not present the saponification is omitted. Evaporate the ethereal solution containing phenols at room temperature. The phenols which may be encountered include thymol and carvacrol (from oil of thyme), eugenol (from oil of cloves), and diosphenol (from oil of buchu). Observe whether the separated phenol shows any tendency to crystallize (thymol, diosphenol). Thymol and diosphenol may be separated from the more " acidic " phenols as follows: Dissolve the mixture in 5 per cent potassium hydroxide solution and distill with steam. Thymol and diosphenol will come over from the alkaline solution while ordinary phenol and most of the eugenol will remain in the distilling flask and can be recovered with ether.

Phenols: Identification

Thymol: Crystalline, m.p. 50.5–51.5°. Identify by U. S. P. test (greenish-blue color on adding one drop each of sulphuric and nitric acids to its solution in glacial acetic acid).

Carvacrol: Liquid isomer of thymol, odor like thymol.

Diosphenol: Crystalline, m.p. 83°, peculiar minty odor. With alcoholic ferric chloride its alcoholic solution gives a dark-green color. Its solutions reduce ammoniacal silver nitrate and Fehling's solution.

Eugenol: Liquid, odor of cloves, m.p. of benzoate, 69–70°. Its alcoholic solution gives a blue color with ferric chloride.

Phenols: Determination

The shrinkage in volume on shaking a measured quantity of the oil with 5 per cent sodium hydroxide solution will indicate the proportion of phenols present.

Ketones: Separation

The oil remaining after the extraction of aldehydes and phenols is now to be used for the separation of ketones. Advantage is taken of the property which ketones have of combining with semicarbazide to form crystalline, more or less difficultly soluble, and difficultly volatile semicarbazones. From $\frac{1}{4}$ to 1 gram of semicarbazide hydrochloride and an equal amount of sodium acetate are dissolved in the least possible amount of water. The oil or its fraction (not over 5 mils) is added and enough

alcohol is stirred in to give a clear solution. (Some NaCl may be precipitated.)

Let the mixture, which should be in a small stoppered flask, stand twelve to twenty-four hours and then dilute with water. If much ketone is present the oil which separates will soon crystallize more or less completely. If crystals separate, filter. In any event separate the oil, transfer it to a distilling flask. and distill with steam until the volatile oil is removed. If any ketone is present a crop of crystals should now separate from the residue left in the distilling flask if it is cooled and shaken. Filter off the crystals in a Buchner funnel and unite with any that may have separated previous to distillation.

To recover the ketones from their semicarbazones, transfer the semicarbazones to a saponification flask, reserving a portion for melting-point and other determinations. Add from 5 to 10 mils of 25 per cent sulphuric acid, stopper the flask, and heat on the steam-bath until the crystals are decomposed. If camphor was present alone or in preponderating amount, it can be seen sublimed into the neck of the saponification flask. Cool and open the flask and note the odor.

Ketones: Identification

Carvone: Liquid, from caraway and spearmint oils, b.p. 230–231°; m.p. of oxime, 72°.

Pulegone: Liquid, from oil of pennyroyal, minty odor, b.p. 222–223°; m. p. of semicarbazone, 168°.

Methone: Liquid, from peppermint, pennyroyal, and buchu oils, minty odor, b.p. 207–208°; m.p. of semicarbazone, 184°.

Camphor: Crystalline, from camphor and rosemary oils, m.p. 175–176°; m.p. of semicarbazone, 236–238°; m.p. of oxime, 118–119°.

Thujone: Liquid, from the oils of thuja, wormwood, tansy and sage, peculiar odor like wormwood, b.p. 200–201°; m. p. of thujone semicarbazone, 186–188°; m.p. of α-thujone semicarbazone, 174–175°.

Methyl nonyl-ketone: Liquid, from oil of rue, odor like oil of rue, b.p. 226°, m.p. +13.5°; m.p. of semicarbazone, 123-124°; m.p. of oxime, 46–47°.

Ketones: Determination

The total quantity of ketones and aldehydes present can be estimated by the hydroxylamine titration method, page 607.

This method will include those ketones which do not react with sodium sulphite or sodium hydrogen sulphite.

ALCOHOLS, ESTERS, ETHERS, AND OXIDES

The volatile oil remaining unacted on by the previous methods of treatment may contain alcohols (as menthol, sabinol, santalol, borneol, and terpineol), esters (as menthyl acetate, and bornyl acetate), and phenol ethers (as methyl chavicol, safrol, anethol, and apiol), or oxides (as cineol).

Previous to the further examination of the oil it should be saponified by boiling with an excess of alcoholic potassium hydroxide in order to decompose any esters present. The alcoholic solution is then diluted with sufficient brine to precipitate the oil completely, and the brine solution can be used for the identification of organic acids derived from esters.

There is no good general method for separating the alcohols as a class, and the further examination will therefore be governed by the judgment of the analyst as to what alcohols are likely to be present.

The primary alcohols, such as geraniol, can be separated by the calcium chloride compounds or as acid phthalic esters, provided they are present in sufficient amount (at least 25 per cent of the mixture).

The conversion of alcohols into esters difficultly volatile with steam will be successful in some cases. Thus by heating menthol with benzoic anhydride for two hours at 160–170° menthyl benzoate is formed, and by distilling the mixture with steam the ester, being less volatile, remains in the distilling flask, is separated, and the menthol recovered by saponifying. The same method is, of course, applicable to any of the more stable alcohols provided they are esterified under these conditions and give benzoates slightly volatile with steam. The identification of the tertiary alcohols is even a more difficult matter, as they are more or less dehydrated on heating with acid anhydrides, but they are not often encountered in a medicinal preparation. When obtained in fairly pure form the alcohols may be characterized by the melting-points of their phenyl urethanes. Sabinol is the alcohol occurring in oil of savin, and since this oil is frequently employed as an abortifacient it should not be overlooked. The best chemical method for identifying sabinol consists in oxidizing it by means of potassium permanganate to α-tanacetogen dicarboxylic acid (m.p. 140°).

Safrol may be found in the higher boiling fractions of the oil, its boiling-point being 233°. The characteristic odor of safrol will serve to direct attention to it, and it can be identified by its oxidation product, α-homopiperonylic acid, which melts at 127–128°. This is obtained by the oxidation of safrol with potassium permanganate. Another phenol ether which may be encountered in medicinal preparations is apiol. This boils at 294°, and will therefore be found in the last fraction of the oil. Apiol has a faint parsley odor. On boiling with alcoholic potassium hydroxide apiol is converted into isopapiol, which melts at 55–56°. Tri-brom apiol

melts at 88–89°. Unless present in relatively large amount its identification, on acccount of its faint odor, is very difficult.

Cineol (b.p. 175°) is separated in the first fractions of the oil. Its odor, which suggests eucalyptus oil, may direct attention to it if there is not too much interfering material. Cineol is an important constituent of eucalyptus and cajuput oils and is often used in medicine in pure form, being more commonly known as eucalyptol.

It combines with phosphoric or arsenic acid giving unstable crystalline compounds from which cineol can be recovered by adding warm water. Its iodole compound (m.p. 112°) is characteristic, but rather difficult to prepare from impure cineol.

Sulphur Compounds, Mustard Oils

The esters of isothiocyanic acid, characterized by their penetrating odor, constitute a special group of sulphur compounds.

Volatile mustard oil obtained from black mustard, Brassica nigra, is mainly allylisothiocyanate, and as this boils at 151° it will be found in the first fraction of the oil and will be recognized by its pungent odor.

Part V

INORGANIC SECTION

CHAPTER XXV

METHODS OF IDENTIFICATION

The inorganic substances used in the formulas of medicines and pharmaceutical preparations are chiefly salts of ammonium, the alkali metals; of the alkaline earth group with the exception of barium; aluminum, iron, manganese, zinc, cerium, bismuth, lead, mercury, silver, gold, copper, antimony and arsenic. The inorganic acids combined in these salts include sulphuric, carbonic, sulphurous, thiosulphuric, phosphoric, phosphorous, hypophosphorous, boric, iodic, hydrofluoric, hydrochloric, hydrobromic, hydriodic, hydrocyanic, hydrogen sulphide, nitric, nitrous, arsenous, chloric, and permanganic. The organic acids will be acetic, citric, and tartaric. Elemental sulphur, carbon, iodin, phosphorus, iron, and mercury are often employed. In addition to the above there are a number of double salts of inorganic and organic bases with organic acids, and of inorganic bases with organic acids.

In testing for any of the chemicals which are included in this group the worker may follow some wellrecognized scheme of qualitative analysis such as that detailed by Newth in his "Manual of Chemical Analysis," Noyes' "Qualitative Chemical Analysis," or Fresenius.

In my work "The Qualitative Analysis of Medicinal Preparations," where I outline a general scheme for the separation of the components of a complex medicine, I show the distribution of both the inorganic and organic substances when the sample is subjected to alcoholic extraction, and the subsequent effect of water on the two large fractions obtained by the alcoholic treatment.

Any procedure for analyzing medicine which recommends a preliminary ashing of the sample should be condemned by the analyst. Such treatment will destroy many valuable constituents and materially alter the condition of others. On the other hand, it is of course recognized that

organic substances often obscure and prevent the characteristic reactions which are essential for the recognition of inorganic substances. For a detailed account of what to do and how to proceed with the complete qualitative analysis of a complex mixture the worker can refer with advantage to my directions for manipulating an elixir.

PRELIMINARY OBSERVATIONS ON RECOGNIZING INORGANIC CONSTITUENTS

The principal inorganic substances or salts of inorganic bases with organic acids used in medicine which are insoluble in water are iodin, mercuric iodide, phosphorus, sublimed sulphur, iron valerinate, bismuth subnitrate, subcarbonate, citrate, and subgallate, cerium oxalate, calcium fluoride, reduced iron, charcoal, red and yellow mercuric oxide, mercurous iodide, mercurous chloride, precipitated sulphur, zinc carbonate, oxide and phosphate, magnesium oxide and carbonate, and a few organic compounds of bismuth, aluminum, calcium, and iron. The first three mentioned are of course soluble in alcohol.

In addition to these a medicinal compound may contain calcium carbonate, sulphate or phosphate, ignited oxides of iron and aluminum, talc, clay, and siliceous compounds, and possibly other heavy inert salts which take part in the architecture of the sample.

Of the above substances, all are soluble in hydrochloric acid except iodin, phosphorus, sulphur, charcoal, calcium fluoride, mercurous iodide, mercurous chloride, ignited oxides of iron and aluminum, talc, and clay. Mercuric iodide does not dissolve in dilute hydrochloric acid, but it goes into solution with the warm concentrated acid. Mercurous chloride is converted into mercuric chloride by aqua regia, mercurous iodide is dissolved, sulphur and phosphorus partly oxidized, and some of the oxides of iron and aluminum dissolved. The organic compounds will be decomposed to a greater or less degree by boiling with the acids and the metals will be found in both the hydrochloric and aqua regia fractions.

The analyst should note carefully any gases evolved, when the unknown product is treated with hydrochloric acid. The carbonates will of course give off carbon dioxide, and if zinc phosphide is present, hydrogen phosphide with its characteristic odor and inflammability will be apparent.

The commoner substances other than those we have already mentioned, which are insoluble in water and acids, are the sulphates of barium, strontium, and lead, the silver haloids, silver, and iron cyanides and tin oxide. Their presence in medicinal products would be most unusual.

In examining the residue insoluble in acids, the presence of free sulphur and charcoal is noted without difficulty. Iodin, unless in large amount, will probably have been dissipated by boiling, and recognized

by the purple vapors evolved. At this point in the well-ordered schemes a test is made for lead and silver. The former is found by treating the residue with ammonium acetate solution, warming, filtering, and testing the filtrate with hydrogen sulphide. If lead is present, as shown by a black precipitate, the residue, both in the dish and on the filter, must be washed with warm ammonium acetate until there is no reaction for lead. The insoluble portion is then tested for silver by warming with potassium cyanide solution, filtering and testing the filtrate with hydrogen sulphide. If silver is found it must be removed by successive treatments with the cyanide reagent. The residue is then washed clean with yellow ammonium sulphide, the filtrate tested for tin and the insoluble matter on the filter washed with water.

Sulphur and carbon should then be burned off in a porcelain crucible and the residue fused in a platinum crucible with a fusion mixture of sodium carbonate 2, potassium carbonate 2, and potassium nitrate 1. After a state of quiet fusion has been attained and the mass cooled, it is leached out with hot water, and in this solution will be found the acids present in the original residue, united to the bases of the flux. Aluminum and chromium might also be present in the aqueous solution in the form of aluminate and chromate. The basic substances present will go into an hydrochloric acid fraction.

The aqueous solution should be acidified with hydrochloric acid and evaporated nearly to dryness in order to convert any silicic acid to insoluble silica. A solution obtained by leaching out the silica residue can then be tested for sulphates, fluorides, aluminates, and chromates. The hydrochloric acid fraction may contain barium, strontium, calcium, iron, aluminum, and chromium. The separation and identification of these metals can be accomplished by following some well-recognized scheme.

CHAPTER XXVI

NON-METALS AND THEIR COMPOUNDS

HYDROGEN. OXYGEN

Hydrogen is not a remedial agent, and neither its recognition or determination are of moment in medicinal analysis.

Oxygen is used as a revivifier and for prolonging life, and the strength of the gas in a cylinder is readily determined by transferring the necessary quantity into a gas burette, and then introducing a measured volume into the alkaline pyrogallol tube of an Orsat or other gas apparatus and noting the amount absorbed by pyrogallol. The solution is made by dissolving 20 grams in 200 mils of potassium hydroxide solution (3 to 10).

PEROXIDES

Hydrogen peroxide, H_2O_2, is used extensively in medicine, and is now an ordinary household article. The metallic peroxides have come into vogue during recent years, but their adaptability is much more limited than was at first anticipated.

Hydrogen peroxide is commonly found in the form of a 3 per cent solution corresponding to 10 per cent by volume of active oxygen. This is the pharmacopœial strength, and is supposed to represent the product sold in packages over the retail counter. It is also sold at 30 per cent strength under the name Perhydrol.

The chief uses of hydrogen peroxide solution are for antiseptic, deodorant, and styptic purposes. It is used in diphtheria, sore throat, eczema, whooping cough, and other conditions requiring an antiseptic wash; for gonorrhea, wounds, old sores, disagreeable runnings from the nostrils and other parts of the body, as a mouth wash and gargle. It is also used hypodermically in cyanide poisoning. In dentistry it is employed for general oral hygiene, as a bleach for the teeth, and for pyorrhea.

Hydrogen peroxide is used to a considerable extent as a hair bleach, and in combination with the phenylene and toluylene diamines in proprietary hair dyes.

Hydrogen peroxide will be found in a great many mixtures which are recommended for mouth washes, gargles, remedies for pyorrhea, and other antiseptic solutions. These preparations often contain other ingredients which are incompatible with peroxide, which soon disappears or becomes

so weak that it has little or no therapeutic value. For instance, an enthusiastic manufacturer will include permanganate, glycerin, alcohol, and hydrogen peroxide in a single mixture, declare them on the label, and then wonder why he is prosecuted for misbranding his product.

Cold creams, claiming to possess valuable properties due to the presence of hydrogen peroxide, have been much in vogue, but in most instances the amount of the active ingredient is either negligible or absolutely *nil*. Of late some of the manufacturers have been substituting sodium perberoate, and in this way a product is obtained which will yield active oxygen when subjected to the peroxide test.

The market was, at one time, flooded with soaps, tooth powders, and pastes featuring a peroxide content, but except in the case of a dry tooth powder containing calcium, magnesium, or zinc peroxide, any peroxide added is soon changed to a more stable body and the peroxide characteristics disappear.

Hydrogen Peroxide, U. S. P.

According to the specifications the standard hydrogen peroxide solution should contain 3 per cent by weight of H_2O_2, corresponding to 10 per cent by volume of active oxygen.

The U. S. P. method for determining the amount of hydrogen peroxide is as follows:

Dilute about 2 grams of Solution of Hydrogen Dioxide, accurately weighed, with 20 mils of distilled water, then acidulate it with 20 mils of diluted sulphuric acid and titrate with N/10 potassium permanganate V. S. It shows not less than 3 per cent of H_2O_2.

Each mil of N/10 potassium permanganate V. S. used corresponds to .0017008 gram of H_2O_2, or to .0008 gram of oxygen. Each gram of Solution of Hydrogen Dioxide corresponds to not less than 17.6 mils of N/10 potassium permanganate V. S.

If it is desired to determine the quantity of oxygen the following procedure will be found satisfactory:

The apparatus consists of a 50-mil side-arm distilling-flask closed with a perforated rubber stopper, through which the delivery stem of a glass-stoppered burette has previously been passed. The side arm of the flask is connected to the nitrometer by means of tightly fitting rubber tubing of any convenient length and securely wired at each end to prevent leakage. The burette is fastened loosely in a Bunsen clamp in such a manner that the burette and flask can be shaken freely on one plane. The nitrometer is filled with water, the level adjusted, and the determination made as follows: Place about 1 gram of finely powdered manganese dioxide or potassium permanganate in the side-arm flask and add 10 mils of 10 per cent sulphuric acid. Dilute 10 mils of the hydrogen peroxide solu-

tion to be tested to 100 mils and place a portion in the burette. After sufficient of the solution is run out to fill the delivery stem of the burette fit the stopper (with attached burette) snugly into the neck of the generating flask, and adjust the level of the water in the nitrometer so as to equalize the pressure within the system. Allow 10 mils of the diluted dioxide solution to run slowly into the generator through the burette. After shaking the flask to liberate the dissolved oxygen as completely as possible again adjust the level and note the temperature and pressure. A correction of 10 mils (the volume of solution run into the generator) is subtracted from the reading, and the remainder reduced to 760 mm. pressure and 20° C. temperature.

The method recommended in the eighth revision for determining the acidity has been the cause of much criticism, and there seems to be no good reason for the figures obtained by an indirect titration. Warren, Kebler and Ruddiman,[1] who made an exhaustive study of commercial peroxides, state:

" Numerous experiments have been made on the determination of the acidity of hydrogen peroxide solutions by the pharmacopœial and other methods, and it has been found that methyl orange could be substituted with advantage for phenolphthalein if the present pharmacopœial method is retained. Experience and experiments furthermore show that the free acidity can readily be determined by direct titration, using phenolphthalein as indicator, and there seems to be no good reason for continuing the use of the present pharmacopœial method."

It is only necessary to add to 25 mils of the hydrogen peroxide about 5 or 6 drops of phenolphthalein test solution (U. S. P.) and titrate directly with N/10 alkali to the development of a light-pink color. Under the conditions this method is accurate to .1 to .2 mil. For practical purposes the test in the Pharmacopœia should be stated as follows:

If to 25 mils of the solution of hydrogen peroxide 5 or 6 drops of phenolphthalein test solution are added, not more than 2.5 mils N/10 KOH should be required to produce a pink color (limit of free acid).

Acetanilid is often used as a preservative, but the amount is small, usually about .1 per cent. This, of course, must be declared on the label and in order to determine the correctness of the declaration the following method may be employed:

In a side-neck flask of 200-mils capacity, place about half a stick of caustic potash or soda (6 to 7 grams). Add about 20 mils of water to dissolve, and then 25 to 30 grams of granulated metallic zinc (the zinc had best be in as fine particles as can be obtained in " granulated " form. There is reason, however, to believe that " zinc dust " is too finely divided for this purpose). Then add a measured amount (not over 50 mils) of

[1] U. S. Dept. Agri. Bur. Chem Bull. 150, 5.

the solution to be tested. Connect the flask, on the one side with a flask to supply steam, arranging the tube to deliver steam near the bottom of the solution; connect on the other side with a condenser. The condenser should deliver into a Peligot bulb tube or some other arrangement by which the distillate is immediately brought in contact with moderately strong hydrochloric acid.

Raise the heat on the flask, slowly, and when nearly half of the contents have distilled over, start the steam passing through. The end of the distillation is a matter of guess. When the anilin is coming over in quantity, fumes are to be seen in the receiver, but for the last portions they cannot be seen. When it is judged that all has come over, detach the receiver and catch what comes over later in a fresh receiver or a beaker, and titrate it separately.

In conducting the titration, standard bromide-bromate reagent is run in from a burette until a faint yellow coloration remains, rotating the flask sufficiently to agglomerate the precipitated tribromanilin.

To prepare the volumetric bromin solution, dissolve 25 grams of caustic potash in 20 to 40 mils of water, cool, and add liquid bromin until it appears supersaturated. Then dilute to about 200 mils and boil out excess of bromin (judged by the color). Cool, and dilute to 1 liter. This should give a solution of which 1 mil = nearly .01 gram acetanilid. Standardize by means of a solution containing .5 gram acetanilid in 200 mils of water, using 30- to 50-mil lots at a time, treated either by distillation in the manner above given, or by boiling with strong hydrochloric acid. Either method was found to give the same result with the same amount of acetanilid.

The detection of hydrogen peroxide or a peroxide in admixture with other drugs is not difficult, but their determination usually presents considerable difficulty, and quantitative methods are still in the experimental stage.

There are three tests for detecting hydrogen peroxide which deserve special mention.

1. An aqueous solution of hydrogen peroxide, even at considerable dilution, will turn a deep-blue color when treated with a few drops of a dilute solution of potassium chlorate followed by a few drops of dilute sulphuric acid, and on shaking with ether the blue color will dissolve in part and color the ether for some time. If the quantity is small the ether should be free from alcohol. This test is not as delicate as some others, but it will show a quantity considerably less than the minimum amount that has any excuse for existing in a product which depends on peroxide for its activity.

2. An aqueous solution of hydrogen peroxide treated with potassium iodide solution and rendered slightly acid with dilute sulphuric acid

becomes yellow, and on shaking with chloroform, the solvent becomes violet owing to the absorption of iodin. This test is probably more delicate than the preceding, and in some instances the color will appear only on long standing.

3. Probably the most delicate test is that with titanium sulphate (1 mg. TiO_2 to 1 mil). A few mils of this reagent are added to the aqueous solution followed by a little dilute sulphuric acid. Hydrogen peroxide gives a yellow color, the shades depending on the quantity present. This test is extremely delicate, and if negative proves beyond a doubt that hydrogen peroxide is absent. A positive test ought always to be supplemented by the two others given above, because the influence of various other organic substances has not yet been determined. This test is of course the reverse of the one used for determining titanium in steel.

In testing for peroxides in liquids, the volatile substances other than water should be evaporated, any acids neutralized with dilute alkali and the solution again made acid with dilute sulphuric, filtering from any precipitate that may have formed. The solution should then be subjected to the three tests given above.

Soaps, cold creams, and tooth pastes are tested as follows: The sample is thoroughly macerated with water and transferred to a Squibb separator of 16 oz. capacity, where it is treated with a slight excess of dilute sulphuric acid. As soon as separation occurs, the clear liquid is filtered into another separator, the magma shaken up with distilled water and the washings filtered into the second separator. This procedure is then repeated and the clear liquid can then be subjected to the above tests.

Tooth powders can be handled in practically the same way. The precipitate will consist in large part of calcium sulphate, but this will remain behind on the filter.

Assay of Metallic Peroxides

One-tenth to three-tenths gram of the material is weighed into a flask, treated with 50 mils of water and 20 mils of dilute sulphuric acid (hydrochloric acid in the case of calcium peroxide), and then titrated with N/10 permanganate.

In the case of sodium peroxide use 1 to 1.5 gram and add gradually to 950 mils of 1 per cent sulphuric acid, making up to 1000 mils with water; 100-mil portions are used for titration.

1 mil N/10 potassuim permanganate = .0036 gram CaO_2
= .002 gram MgO_2
= .003786 gram Na_2O_2
= .0061 gram SrO_2
= .0048 gram ZnO_2

NITROGEN AND ITS ACIDS

Nitrogen as a free element is of no moment in our work, but its identification, as one of the elements in an organic compound, is of considerable importance, and in some instances where a new and totally unfamiliar substance is under examination, its determination will be necessary. The methods for detecting and estimating the percentage of nitrogen in organic compounds are fully described in Gattermann's "Practical Methods of Organic Chemistry," to which the worker is referred.

Nitrogen Oxyacids

Nitrate of potassium and nitrate of silver are the two salts of nitric acid which have an important place in medicine. The former is a diuretic, and the latter an antiseptic and astringent. The estimation of nitrates follows more conveniently from the determination of the metallic element.

The alkali nitrates have a limited use in therapeutics, and amyl and ethyl nitrite, the latter in sweet spirit of nitre, are of considerable importance. The method of determining the nitrite radicle and estimation of the ester has already been given in detail on page 734.

Nitrites may be determined by titration with permanganate according to the equation $5HNO_2+K_2Mn_2O_8+3H_2SO_4=5HNO_3+K_2SO_4+2MnSO_4+3H_2O$. If the reagent is standardized with iron, 4 atoms of iron correspond to 1 molecule of N_2O_3. For 1 part NO_2 at least 5000 parts of water should be present. The sample is dissolved in water slightly acidulated with sulphuric acid, the permanganate added till the oxidation of the nitrous acid is nearly completed, the solution then made strongly acid and finally permanganate is added to light-red coloration.

THE HALOGENS AND HALOGEN ACIDS

With the exception of iodin, none of these elements by themselves have an extended application in medicine. Bromin water and chlorin water are preparations used to a slight extent where drastic disinfectants are needed, such as in cancerous conditions, foul discharges, boils, and ulcers, smallpox, diphtheria, and venereal disease.

The use of iodin is on the increase. It is a popular application in dentistry and nose and throat work, where it functionates as an antiseptic and cleansing agent, and possibly as a tonic. It is used in erysipelas and other skin diseases, in enlarged and scrofulous glands, venereal discharges, and in many other conditions requiring an antiseptic.

The official liquid preparations of iodin are the tincture, which contains 70 grams of iodin and 50 grams of potassium iodide in 100 mils of alcohol

(95 per cent), and the compound solution, containing 5 grams of iodin and 10 grams of potassium iodide in 100 mils of water. These preparations are often too irritating to the membrane to be used without modification, and hence will be diluted with water or glycerin. Inhalants are made up with a neutral oil base containing different percentages of iodin sometimes up to 2 per cent, with menthol, thymol, eucalyptol, camphor oil of cassia, sassafras, etc.

Besides the above-mentioned common methods of dispensing iodin in solution, preparations have recently appeared which contain no iodides or glycerin, but which depend upon hydriodic acid and alcohol to keep the iodin in solution. These solutions are capable of considerable dilution without the precipitation of iodin.

Iodin ointments are popular. The iodin is usually dissolved in glycerin and potassium iodide, and then mixed with the base. Ammonium oleate mixes readily with iodin and glycerin and ammonium iodide, and proprietary preparations containing these substances in a petrolatum base are widely exploited.

Bromin chloride, BrCl, is a reddish-yellow, mobile, volatile liquid, unstable, losing chlorin at 10°. It has been used in cancerous conditions. Iodin monobromide, IBr, and monochloride, ICl, are solids. Iodin pentabromide, IBr_5, and tribromide, IBr_3, are dark-brown liquids which are employed in dilute sprays for diphtheria and other conditions requiring an antiseptic application to the mucous membrane.

Characteristics and Qualitative Tests for Elementary Halogens.—Chlorin is well known as a greenish-yellow gas, with a characteristic suffocating odor, and an irritating action on the mucous membrane of the nose and throat. Its solution in water is yellow in color and the addition of a bromide or an iodide, bromin or iodin are liberated, and will dissolve in chloroform with their characteristic color. Chlorin water is a powerful bleaching agent and will decolorize indigo solutions.

Bromin is a dark, brownish red, volatile liquid, vaporizing at the ordinary temperature. Its action on the membrane of the nose and throat and eyes is powerful, but the effect may be ameliorated by exposing the inflamed parts to the vapors of chloroform. Its bleaching action is less than that of chlorin. It gives a yellow color with starch and its aqueous solution is reddish. It dissolves in chloroform with a reddish-brown color and will liberate iodin from solutions of iodides.

Iodin is a solid, steel-like, and shiny in appearance, and readily passes into a deep violet-colored vapor at ordinary temperature, and on heating. It fuses, but will volatilize without melting. It is only slightly soluble in water, but dissolves readily in alcohol and other organic solvents, hydriodic acid, and iodide solutions. Its solution in chloroform is violet deep-purple or almost black, depending on the quantity present. With

cold starch paste iodin gives an intense indigo-blue color which will disappear on heating and again appear on cooling.

Quantitative Analysis of Preparations Containing the Free Halogens.—Iodin can be titrated directly with N/10 thiosulphate, using starch as an indicator.

For assaying tincture of iodin the Pharmacopœia method recommends using 5 mils, mixed with 25 mils of water, which will require about 27.25 mils N/10 thiosulphate for decolorization.

The compound solution of iodin is assayed by weighing 6.3 grams and titrating with the same reagent, which should require about 24.75 mils.

$$1 \text{ mil N/10 } Na_2S_2O_3 = .01259 \text{ gram iodin}$$

In making an assay of the more common iodin mixtures the procedure will depend somewhat upon the nature of the ingredients, which will have to be identified by a previous qualitative examination. The directions here given can be used for a mixture containing free iodin, free hydriodic acid, an iodide, alcohol, and water. Glycerin will not interfere with the tests, but no satisfactory method is available for its own estimation except in an approximate manner, and the analyst is referred to that portion of the work which discusses glycerin specifically.

If desired a weighed quantity can be made up to a definite volume and aliquots taken for the tests. If the specific gravity is determined and measurements made at the same temperature the sample may be measured. Twenty-five mils are transferred to a 100-mil graduated flask and made up to the mark. An aliquot amounting to 25 mils is titrated with thiosulphate in order to determine the free iodin, and in the decolorized solution any free hydriodic acid is determined by titrating with N/10 alkali. 1 mil N/10 KOH = .012690 HI. A second aliquot of 25 mils is transferred to a separatory funnel, diluted with water and shaken out with chloroform, if the iodin fails to entirely leave the aqueous liquid, collect the chloroform in another separatory funnel and repeat until decolorized. Combine the solvents and wash with water, discarding solvent and returning wash water to the main liquid. Filter and wash. Then neutralize filtrate and washings and concentrate over the steam-bath. Filter if not clear and in the filtrate determine the iodin by precipitating with silver nitrate in the presence of dilute nitric acid. Collect the silver iodide on a tared Gooch, wash thoroughly and weigh. From the total iodin found deduct that due to hydriodic acid and calculate the rest to the iodide salt present. Alcohol must be determined in a separate portion of the original sample. In order to do this proceed as directed for the determination of alcohol in galenical mixtures, page 2, first destroying the free iodin with crystalline thiosulphate and then neutralizing any free acid.

Free iodin in ointments and inhalants of an oily nature can be determined by transferring the weighed sample to a flask possessing a ground-glass stopper and a long air condenser. Alcohol containing 10 per cent potassium iodide is then added and the flask warmed until the ointment has melted, and then gently agitated. If the heat tends to drive the iodin beyond the lower half of the air cooler, introduce a little aqueous potassium iodide through the cooler and continue the agitation. Cool, remove the stopper, and transfer alcoholic liquid to a closed flask, washing out flask and residue with alcohol containing potassium iodide. Repeat digestion with alcoholic potassium iodide and then wash out condenser and titrate the solution with N/10 thiosulphate.

While the determination in medicinal preparations of free chlorin or bromin is seldom a matter of moment, this may be accomplished by adding an excess of potassium iodide solution and titrating the liberated iodin with thiosulphate. Each mil

$$N/10\ Na_2S_2O_3 = .007936 \text{ gram Br}$$

$$= .003518 \text{ gram Cl.}$$

Sulphur Iodide. U. S. P. Assay.—.5 gram of finely pulverized sulphur iodide together with 1 gram potassium iodide is dissolved in 20 mils of water (sulphur separating), not less than 28 mils N/10 $Na_2S_2O_3$ should be required for complete decolorization of the mixture using starch as indicator.

Assay of Iodin Ointment, L. H. Freed.[1]—*Free Iodin.*—Carefully clean, dry, and tare a 120-mil Erlenmeyer glass-stoppered flask and accurately weigh into it from 3 to 5 grams of ointment, using a glass rod for transferring it. Add 30 mils chloroform, shake the flask a few minutes until the ointment is apparently dissolved. Then add 30 mils of distilled water, shake, and immediately titrate with N/10 sodium thiosulphate.

Potassium Iodide.—Five grams are weighed into an ordinary 250-mil Erlenmeyer flask and attached to a distillation apparatus, using as a receiver a 250-mil glass-stoppered Erlenmeyer containing 1 gram potassium iodide dissolved in 30 mils distilled water, and 30 mils chloroform. Allow the end of the condenser tube to dip into this mixture. Make all connections air-tight, using rubber stoppers. Mix 5 mils sulphuric acid with 150 mils of distilled water; add the acid mixture quickly into the flask followed by a few pieces of pumice which have previously been heated to redness and dropped into cold water. Finally, add about 5 grams of ferric alum. Place upon a wire gauze and apply direct flame very slowly at first, until the purple vapors of iodin have all distilled over. The

[1] J. Amer. Pharm. Assn., 1915, 4, 621.

iodin will sometimes condense in the tube and not go down into the receiving flask; if this happens move the flame and allow the liquid to run back into the tube and dissolve the iodin. Replace the flame and continue distillation until an oily substance comes over. Discontinue the distillation by first removing the receiving flask, then remove the flame and wash out condenser tube end with 20 mils water. Immediately titrate with N/10 thiosulphate. The result is the total iodin, from which, after subtracting the amount of free iodin, the quantity of potassium iodide is calculated.

Rapid Method for Separation and Estimation of Iodin.—This method, discovered by Seeker and Mathewson,[1] was first used for estimating iodin in Erythrosine, but it is applicable to other organic compounds, and useful in assaying iodin in inorganic mixtures containing chlorin and bromin. Dissolve .3 to .4 gram of the sample in 5 mils 10 per cent sodium hydroxide, add 35 mils 7 per cent, potassium permanganate, cover with a watch-glass and add 10 mils concentrated nitric acid. Heat on a steam-bath, keeping covered until all spattering ceases, then remove cover and evaporate to dryness. Treat the residue with 5 mils permanganate and 5 mils nitric acid, and again evaporate. Dissolve the residue in 50 mils water, 5 mils nitric acid, and 40 mils saturated sulphur dioxide solution. Then add excess silver nitrate, boil till sulphur dioxide is expelled, and the silver iodide has flocculated, and filter and weigh the latter as usual.

HALOGEN ACIDS

Of considerably greater importance in medicine than the elemental halogens themselves are the halogen acids, and more particularly the salts of these acids. There are two general classes of these acids, halogen hydrides and halogen oxyacids.

To the first belong hydrochloric, hydrobromic, hydriodic, and hydrofluoric acids. The free acids, with the exception of hydrofluoric, which boils at 19.5° C., are fuming gases at the ordinary temperature. They dissolve readily in water, and their solutions constitute the different grades and strengths of acids of commerce. Many of the salts of the first three are well-known remedies and they will often be found in the analysis of complex mixtures. The identification of these acids has already been discussed in the general scheme for arriving at the composition of the inorganic constituents of a given product.

Hydrochloric acid of the U. S. P. is an aqueous solution of about 31.5 to 32 per cent HCl gas. Diluted it may be used as an antiseptic, antipyretic, and caustic in fevers, dyspepsia, syphilis, eczema, psoriasis, etc. As a popular remedy it should be anticipated in preparations recommended

[1] U. S. Dept. Agri. Bu. Chem. Circ., 65.

for impaired digestion, and it will sometimes be found accompanying all of the digestives and stomachics in tablets and liquid preparations. Chlorides of the different metals find application over the entire field of medicine.

Hydrobromic acid is marketed in different strengths, but the official acid is the dilute, and contains 10 per cent by weight of HBr. It has a limited use in allaying nervous conditions, especially of an acute or violent nature. The bromides are much more stable and are extensively used in medicine.

Hydriodic acid is official in the Pharmacopœia as a 10 per cent solution, but acid of much greater strength is obtainable. If made according to the specifications of the standard, the solution will contain a small quantity of hypophosphorus acid and perhaps a little tartaric acid. Its chief use is for the preparation of syrup hydriodic acid, which contains about 1 per cent by weight of HI.

Hydriodic acid is used in rheumatism, bronchitis, asthma, syphilis, obesity, psoriasis, eliminating mercury and arsenic from the system, and as a tonic. The metallic iodides are in the aggregate probably the most extensively used chemicals in the field of medicine. Potassium iodide will be found in many of the advertised asthma and hay fever "cures" and in the sarsaparillas.

Quantitative Estimation of the Free Acids and Acid Radicles.—The estimation of free hydrochloric acid in aqueous solution may be accomplished by titrating with standard alkali, and the other halogen acids can also be determined in like manner.

The Pharmacopœia does not direct that either hydrobromic or hydriodic acid shall be titrated directly with alkali. The former is determined after neutralizing with ammonia, by titrating with silver nitrate, and the latter by an indirect method detailed below.

For determining the quantity of halogen in a mixture containing the free acids or an aqueous solution of a chloride, bromide, or iodide, there is no better method than that of precipitating with silver nitrate in presence of an excess of dilute nitric acid, boiling, filtering onto a tared Gooch, and weighing the silver compound. The details of this manipulation are well known to a worker in quantitative methods. It is applicable to complex medicines, and may be employed after the removal of organic substances by shaking out procedures, provided, of course, that no halogen acid or compound has been introduced during the manipulation. Before precipitating with silver nitrate the solution should be boiled for ten to fifteen minutes after the addition of concentrated nitric acid. The quantity of the acid added should not be great enough to cause a decomposition of any iodide or bromide. After boiling, the silver nitrate is added, and when the precipitate has agglomerated, it is filtered onto a tared Gooch and well washed with water and finally with alcohol to remove

organic products of decomposition. From the weight of the silver compound the acid or salt can be readily calculated.

The determination of the purity of a salt of a halogen acid by the U. S. P. method may be accomplished as follows.

A weighed amount of the salt is dissolved in water, the solution treated with 2 to 3 drops of potassium chromate, and then titrated with N/10 silver nitrate until a permanent brownish-red color is obtained.

This procedure as applied to the following salts may be summarized.

	Amount Taken, Grams	Made up to	Aliquot Mils	Mils N/10 $AgNO_3$	Purity, Per Cent	1 mil N/10 $AgNO_3$ equals gram
HBr	10	100 mils neutralize	8	10	10	
NH_4Br	3	100 mils	10	31.6	97	.009729
NH_4Cl	1	100 mils	10	18.7	99.5	.005311
LiBr	1	100 mils	20	22.5–23.9	97	.008634
KBr	0.3	50 mils	50	24.6–25.85	97	.011822
KI	0.5	10 mils	10	30–30.8	99	.016476
NaBr	0.3	50 mils	50	28.5–30	97	.010224
NaCl	1	100 mils	10	17.05	99	.005806
NaI	0.5	10 mils	10	33–34.6	98	.014878
$SrBr_2+6H_2O$	0.5	50 mils	50	27.4–29.4	97	.017647
ZnBr	0.3	10 mils	10	26–26.8	97	.011181

For hydriodic acid and some of the iodides the Pharmacopœiá recommends a different procedure. A weighed quantity in aqueous solution is treated with a known excess of N/10 silver nitrate, 5 mils of ferric ammonium sulphate test solution and 3 to 4 mils of nitric acid free from nitrous fumes. After thorough shaking it is titrated back with N/10 potassium sulphocyanate until a permanent reddish-brown tint is obtained.

The application of this method to pharmacopœial chemicals may be noted below.

	Amount Taken, Grams	Made up to	Aliquot, Mils	N/10 $AgNO_3$, Mils	N/10 KSCN	1mil N/10 $AgNO_3$ equals
HI	2.54	50 mils	50	25	not more than 5 mils	0.5% HI
Syrup HI	31.73	50 mils	10	8	not over 3 mils	0.2% HI
Syrup FeI_2	10	100 mils	15.4	6	not over 1 mil	1.0% FeI_2
SrI_2+6H_2O	0.5	100 mils	100	25	1.7–3.1	Purity 98%
ZnI_2	0.5	20 mils	20	35	3.4–4	Purity 98%

HALOGEN OXYACIDS

Hypochlorous acid, HClO, is familiar to the pharmaceutical chemist in the form of its calcium salt known as bleaching powder, and in the form of a solution of its sodium salt, which is called chlorinated soda or Labarraque's solution. Both of these salts are unstable and readily part with their chlorin even under the influence of carbon dioxide. They also yield chlorin when treated with dilute acetic and mineral acids, and in this way are sharply distinguished from chlorides and chlorates. When silver nitrate is added to a solution of sodium hypochlorite there is a precipitation of silver chloride representing two-thirds of the silver. the balance being dissolved probably as silver chlorate.

$$NaOCl + AgNO_3 = AgClO + NaNO_3$$

$$3AgClO = AgClO_3 + 2AgCl$$

Sodium hypochlorite solution is usually sold unmixed with any other drug. The Pharmacopœia directs that it shall contain not less than 2.4 per cent available chlorin. The activity may be determined by transferring .5 to .7 gram weighed out by means of a dropping bottle to an Erlenmeyer flask, diluting with 50 mils of water, adding 2 grams potassium iodide and 10 mils hydrochloric acid and titrating the iodin with N/10 thiosulphate.

The solution is used chiefly as a disinfectant and antiseptic in cases of malignant nature, scarlet fever, typhoid, scrofula, syphilis, and where there are foul and offensive discharges.

Method of Assay of Calcium Hypochlorite, U. S. P.—Introduce into a stoppered weighing bottle between 3 and 4 grams of the sample and weigh accurately; triturate thoroughly with 50 mils of water and transfer to a graduated 1000-mil flask, adding rinsings and make up to volume. After shaking allow the sediment to settle and decant 100 mils. Add 1 gram KI and 5 mils diluted hydrochloric acid and titrate with N/10 $Na_2S_2O_3$. Multiply the number of mils consumed by .3518 and divide the product by $\frac{1}{10}$ the weight of the sample; the quotient represents the percentage of available chlorin present.

The acids, chloric, $HClO_3$, bromic, $HBrO_3$ and iodic, HIO_3, differ in stability in the opposite order to that usually shown by halogen compounds. Iodic acid is a comparatively stable solid, but is readily reduced by sulphur dioxide or hydrogen sulphide with liberation of iodin, and it reacts with hydriodic acid, all of the iodin being set free, $HIO_3 + 5HI = 3H_2O + 3I_2$. This reaction is of value in detecting the presence of an iodate when mixed with an iodide, for by dissolving in water and adding acetic acid the liberated acids react and the iodin is set free.

The most important medicinal chemical representing this group is

potassium chlorate. It has an extensive use as a household remedy for sore throat and is also used in diphtheria, stomatitis, and diseases of the mucous membrane. It will be found in aqueous mixtures intended as a spray in nasal troubles, hay fever, asthma, and the like, and mixed with opium extract for hemorrhoids. In the powder form it occurs mixed with other substances as a dusting mixture for wounds and ulcers.

Potassium chlorate is often combined with ammonium chloride in throat tablets and with sodium chloride in nasal sprays.

Sodium chlorate is also in general use, and magnesium chlorate has a slight use.

Having detected the presence of a chlorate in the regular scheme of analysis, and there being no other halogen acid present, the chlorate may be determined by dissolving a weighed sample in water, adding dilute sulphuric acid and a piece of zinc and allowing the reaction to continue for thirty minutes. The solution is then filtered from any undissolved zinc, the filter paper washed and the filtrate neutralized with sodium carbonate and the chlorin then determined by precipitation with silver nitrate in the presence of nitric acid. The amount of $KClO_3$ may be obtained from the factor .8551, $NaClO_3$ .7445.

The determination of the chlorides and chlorates in admixture may be accomplished by weighing out the sample into a graduated flask, dissolving in water, and determining the chloride in an aliquot by precipitating with silver nitrate. An aliquot of the same quantity is then treated with zinc and sulphuric acid as described above and the total chlorin determined. The silver nitrate representing the chlorate is then easily figured and calculated to the chlorate.

Bromates are unimportant medicinally. Iodates of sodium and potassium are used sometimes both as substitutes for chlorates and iodides. They are used externally in trachoma, corneal infiltration, and torpid ulcers and internally for acute and chronic muscular rheumatism.

Iodin pentoxide, I_2O_5, so-called "Anhydrous Iodic Acid," is a white powder soluble in water with formation of IH_2O_3. It is used internally in gastric hemorrhage and vomitings and externally in nose and throat work and venereal disease. It is a powerful oxidizing agent.

Iodic acid is a colorless crystalline powder soluble in water and used medicinally in aqueous solution for the ailments mentioned above.

Perchloric acid, $HClO_4$, in the form of its potassium salt is used as an antipyretic and antiperiodic in pernicious fevers and malarial conditions. The perchlorates are more stable than the chlorates. Sulphuric acid liberates the free acid, which is a colorless, fuming, corrosive, volatile liquid. No yellow color appears in this test as is the case with chlorates. Hydrochloric acid has no action on perchlorates, which is in sharp distinction from its action on chlorates.

ORGANIC HALOGEN COMPOUNDS

Organic compounds of iodin are commonly employed as medicinal agents. The iodin in these substances can often be determined by boiling a solution of the substance with dilute nitric acid and then precipitating with silver nitrate, filtering and thoroughly washing with alcohol and then water (see Emery's Method for Determining Iodin in Antipyrin periodide, described on p. 801. It often happens that this procedure will not suffice to bring the iodin into proper condition for precipitation with silver nitrate and in the event of such a contingency recourse must be made to a Carius combustion. Again it will be simply necessary to saponify with alcoholic potash (ethereal salts), see chloroform and iodoform, p. 742–744.

The determination of chlorin and bromin in organic combination follows the same general procedure.

SULPHUR AND SULPHUR ACIDS

The Pharmacopœia recognizes three forms of sulphur, the sublimed or flowers of sulphur, the precipitated or lac sulphur, often impure from the presence of calcium salts, and the washed. One of the commonest sulphur preparations is the combination with potassium bitartrate. Sulphur is employed in atonic gout, chronic rheumatism, chronic catarrh, asthma, piles, and cutaneous affections, and is dispensed usually in the form of lozenges and tablets.

Sulphur is insoluble in water and precipitated sulphur does not dissolve in alcohol. Sublimed sulphur is somewhat soluble in alcohol. The identity of the element is determined by its burning with a pale-blue flame, producing sulphur dioxide, which has a characteristic odor and turns potassium iodate starch paper. When heated in a test-tube, sulphur melts and boils off as a brownish-yellow vapor, which condenses to brown drops on the moderately hot parts of the tube, and as a yellow sublimate on the upper and cooler part. Nitric acid oxidizes sulphur to sulphuric acid with evolution of nitrogen peroxide.

When elemental sulphur is combined with substances soluble in water, it is readily determined by treating the ground substance with water, filtering through a Gooch, drying, and weighing the residual sulphur. When sulphur is combined with charcoal or other substances insoluble in water or carbon bisulphide, the sample should be ground and extracted with carbon bisulphide, the solvent collected in a tared dish, evaporated, and the residue weighed.

Free sulphur in complex formulas containing vegetable drugs can be determined by oxidation with nitric acid in a Carius tube. The sample should be ground and extracted with hydrochloric acid, filtering through a Gooch, and the residue is then transferred to the tube. Sufficient fuming

nitric acid is added to cover the material, the open end of the tube drawn out to a thick-walled capillary and sealed off. The tube is introduced into a Carius combustion furnace and heated from four to ten hours, raising the temperature gradually from 100 to 300°. After cooling *in the furnace*, the pressure is relieved by applying a flame to the capillary. The end of the tube is broken off, the contents washed out, the diluted liquid filtered, and the sulphate precipitated by barium chloride. The barium sulphate is filtered, washed, ignited, and weighed.

Hydrogen Sulphide

Hydrogen sulphide water is occasionally employed as a remedy in certain types of tuberculosis. Barium sulphide is a depiliatory and will be found mixed with zinc oxide and starch. Sulphurated lime, which is a mixture of calcium monosulphide and sulphate, is also used as a depiliatory and as an alterative. It will be found in pills and tablets and is employed in measles, scarlet fever, erysipelas, influenza, acne, and furuncular eruptions.

The determination of sulphide sulphur in substances of this nature can be made by the method of assay for calcium sulphide in the Pharmacopœia.

Introduce about .2 gram of calcium sulphide, accurately weighed, into a glass-stoppered bottle or flask; add 50 mils of distilled water, mix, and quickly introduce 30 mils of a 10 per cent ammonium chloride solution and immediately stopper the flask. Agitate the contents for a few minutes, add quickly 20 mils of a 10 per cent cadmium chloride solution, immediately insert the stopper and again agitate well for a few minutes. Then add 5 mils of acetic acid, heat the mixture on a water-bath for fifteen minutes, decant the supernatant liquid through a filter, agitate the remaining precipitate with 10 mils of diluted acetic acid, transfer the precipitate to the filter, and wash with 10 mils of diluted acetic acid. Return the filter and precipitate to the original flask, add 50 mils of N/10 iodin V. S. and 20 mils of a mixture of equal volumes of hydrochloric acid and water. Stopper the flask and agitate it vigorously for a few minutes, and then titrate the excess of iodin with N/10 sodium thiosulphate V. S. It shows not less than 55 per cent of CaS.

Each mil of N/10 iodin V. S. used corresponds to .003607 gram of CaS. Each gram of crude calcium sulphide corresponds to not less than 152.5 mils of N/10 iodin V.S.

SULPHUR OXYACIDS

The sodium and some of the potassium salts of the sulphur oxyacids are used quite extensively in medicine. Sulphate of magnesium is a well-

known household remedy. Certain proprietary sulphur remedies consist of mixtures of the alkali and alkaline earth salts of one or more of all of the sulphur acids and were formerly labeled "Soluble sulphur." To distinguish the several combinations of sulphur acids a solution may be examined as follows: The sulphide is separated by agitating the solution with lead or cadmium carbonate and filtering. Barium chloride is then added to the filtrate and the sulphate and sulphite precipitated. After filtering, the filtrate is treated with hydrochloric acid and the thiosulphate will be decomposed with precipitation of sulphur and evolution of sulphur dioxide. The mixed sulphates and sulphite of barium are then treated with hydrochloric acid which will dissolve the sulphite, and on filtering and adding chlorin water to the filtrate the sulphurous acid will be oxidized to sulphuric acid with precipitation of barium sulphate.

The sulphur as sulphate in an unmixed medicinal chemical is usually determined by the well-known procedure of precipitating with barium chloride in presence of hydrochloric acid, filtering onto a Gooch and weighing or by ignition on a filter paper.

Sodium sulphite is a salt which, on standing, will gradually oxidize to sulphate. The purity of a sample is determined by dissolving in recently boiled water and titrating with iodin in presence of hydrochloric acid. As a remedy it is employed as a germicide and anti-fermentative and should be looked for in tablets recommended for sour stomach and indigestion. Galenicals of this class often contain Nux Vomica and ipecac, and aqueous solutions prepared directly cannot be titrated with iodin. Sodium sulphite is sparingly soluble in alcohol and hence if its determination is desirable an aqueous solution of the tablet is filtered, oxidized by boiling with chlorin or bromin water, and the sulphate precipitated with barium. In case a water-soluble sulphate is simultaneously present, the filtered aqueous solution is made up to a definite volume, the sulphate determined in an aliquot and a second portion subjected to the chlorin oxidation.

Thiosulphate of sodium is an antiseptic and germicide, and is employed in parasitic skin diseases, sore mouth, diphtheria, diarrhea, typhoid fever, dyspepsia, etc. The purity of a sample is determined by titration with iodin in neutral solution. $2Na_2S_2O_3+I_2=2NaI+Na_2S_4O_6$. If this salt occurs in admixture and titration is not feasible, it may be converted into the sulphate by means of chlorin or bromin water and then determined.

PHOSPHORUS AND ITS ACIDS

Phosphorus, as an element, is a component of a class of medicines known as lost-manhood restorers, and will be found in pills, tablets and elixirs alone and combined with Nux Vomica, damiana, cantharides, coca cinchona alkaloids, iron salts, aloes, Digitalis, belladonna, Cannabis sativa,

zinc, and other valerianates, opium alkaloids, ipecac, and metallic phosphides. It is also combined with cod-liver oil in capsules. The analyst who undertakes the examination of galenical preparations will often meet with phosphorus in combination with one or more of these drugs. This element is also found to a considerable extent in rat poisons, and its detection is of considerable importance in toxicological investigations.

Phosphorus used in medicine is the yellowish stick form. Its detection is simple, especially when it occurs in elixirs, for it distills when the mixture is boiled, and in making an alcohol determination it will be found in the distillate. It is good practice, after determining the specific gravity of the distillate, to add a slight excess of chlorin water and allow the solution to stand an hour or more. If phosphorus is present it is oxidized to phosphoric acid, and on boiling off the excess of chlorin and adding ammonium molybdate a yellow precipitate will appear.

If phosphorus is suspected in pills or tablets it can be dissolved by triturating the ground material with alcohol. The alcoholic solution is filtered, diluted with water, and subjected to distillation, whereupon the phosphorus will appear in the distillate. In the general scheme of qualitative analysis a small portion of the alcoholic extraction should be reserved for the above test.

Ewe and Vanderkleed [1] have described a simple method for determining free phosphorus in rat pastes, which is applicable to tablet and other preparations containing the substance in the elemental state. The sample amounting to about a gram in the case of a rat paste, and considerably more of a galenical is placed in a distilling flask connected with a carbon dioxide generator and a condenser, the condenser being connected with a 300-mil Erlenmeyer flask containing 50 mils of 3 per cent silver nitrate solution. The Erlenmeyer flask is connected in series with two U tubes containing 3 per cent silver nitrate solution. All connections exposed to the phosphorus should be of glass or cork covered with plaster of paris. A stream of carbon dioxide is passed through the apparatus for twenty minutes and the joints examined for leaks with flexible collodion; 125 mils of cold, freshly boiled distilled water containing 2 mils of sulphuric acid are introduced into the flask containing the sample by means of the tube which leads to the carbon dioxide generator. The current of gas is continued, and the flask gently heated until, after about three hours, practically all of the liquid has been distilled into the silver nitrate solution. The condenser is allowed to become hot from the distillation, and the generator is disconnected and the flame removed. All of the silver nitrate solution is then collected in the Erlenmeyer flask, using nitric acid to dissolve any black precipitate in the U tubes. Fifteen mils of nitric acid are added to the mixture, boiled for five minutes and a slight excess of hydro-

[1] J. Amer. Pharm. Assn., 3, 1914, 1684.

chloric acid to precipitate the silver. After boiling until the silver chloride separates out completely, the flask is cooled and the liquid filtered and concentrated to 150 mils. It is then cooled, excess of ammonia added, followed by nitric acid, the phosphate precipitated by molybdate, and the determination completed by the customary procedure.

Estimation of Yellow Phosphorus.—Engelhardt and Winters [1] give the following method: The phosphorus, deprived of any oxidation products by scraping, is dried in an atmosphere of carbon dioxide, weighed, dissolved in chloroform free from air, and made up to volume, the solution adjusted so that 10 mils corresponds to .03656 gram of phosphorus. Ten mils of the solution are received in a bottle with 15 mils 10 per cent copper nitrate from which the air had been expelled by heating; the air in the bottle replaced by carbon dioxide, and the mixture shaken for one-quarter hour. Hydrogen peroxide is added, the mixture shaken until the black color of the copper phosphide disappears, the aqueous solution separated, the chloroform washed twice with 15 mils water, the combined aqueous solution and wash-waters after the addition of nitric acid evaporated to 5 mils testing from time to time for unoxidized phosphorous acid. When oxidation is complete the phosphoric acid is estimated in the aqueous liquid as mangnesium pyrophosphate.

Phosphorus Resin.—Four grams of the resin (accurately weighed) are dissolved in 50 mils air-free chloroform in a separator, 20 mils air-free water added, the air in the separator replaced by carbon dioxide and the mixture shaken for one-quarter hour. An aliquot of the chloroform solution is then drawn off and treated with copper nitrate as given above.

Phosphorus Paste.—About 1 gram of the paste (accurately weighed) is mixed in a bottle filled with carbon dioxide, with 25 mils of air-free chloroform and 25 mils of air-free water, and the mixture shaken for fifteen minutes. After separation the aqueous layer is siphoned off, and the chloroform shaken once more with 15 mils of air-free water to remove the last traces of oxidation products of the phosphorus. The water is again separated, the chloroform solution treated with copper nitrate solution, and the estimation continued as above.

Spirit of Phosphorus.—Twenty-five mils of spirit are mixed with 50 mils air-free chloroform and 50 mils water, the mixture well shaken, and when complete separation has taken place the chloroformic solution drawn into a flask filled with carbon dioxide. The aqueous solution is shaken with two more portions of 25 mils each of chloroform, the combined chloroformic liquids treated with copper nitrate in the usual way and the estimation completed as above.

Phosphorus Pills.—A quantity of pills equivalent to about one grain of phosphorus is mixed in a bottle with 25 mils of air-free water and 100

[1] J. Am. Pharm. Assn., 1915, 4, 451.

mils of air-free chloroform. The air in the bottle is replaced by carbon dioxide and the mixture well shaken until the pills are disintegrated. After allowing the liquids to separate as much as possible the aqueous layer is siphoned off. The mixture is then shaken with sufficient tragacanth to eliminate the remaining water, an aliquot of the chloroformic solution filtered off, treated with copper nitrate, etc.

Elixir of Phosphorus.—Twenty-five mils of the elixir are mixed with 50 mils air-free water in a separator, the air displaced by carbon dioxide, and the mixture shaken with 50, 25, and 25 mils air-free chloroform. The combined chloroformic liquids are shaken out once with 10 mils of air-free water to wash out any phosphorus oxidation products, separated and the chloroform solution treated with copper nitrate in the regular way.

PHOSPHORUS COMPOUNDS

The phosphorus compounds occurring in medicinal preparations consist of the salts of phosphoric, hypophosphorus and glycerophosphoric acids, phosphides and organic substances containing phosphorus in combination. Plant extracts contain phosphates and probably organic substances containing phosphorus. The coatings and subcoatings of pills and tablets sometimes contain phosphates, so that the presence of phosphates does not necessarily indicate that it is there as a remedial agent.

Of the phosphides, the zinc compound is the only one of importance, and it may occur in the same class of mixtures that elemental phosphorus does and the remedies are used for the same purpose.

Sodium phosphate is an important drug. Calcium phosphate is used as a remedy and is an important constituent of dentifrices. It is also employed as a mechanical agent in molding pills and tablets.

Iron phosphate and pyrophosphate are important and potassium phosphate is used as an alterative. Magnesium phosphate is of lesser importance, as are the lactophosphates of the alkalies and alkaline earths, which are probably mixtures of the salts of the two acids, lactic and phosphoric. The glycerophosphates have been treated under ethereal salts.

The hypophosphites of the alkalies, certain of the alkaline earths, and iron and manganese are important medicinal agents and are to be found largely in reconstructive tonics. The phosphites are of no importance in this work.

The most delicate reaction of the phosphates is the production of the canary-yellow precipitate, when a solution of the substance in the presence of nitric acid is warmed with an excess of ammonium molybdate. Silver nitrate gives a yellow precipitate with soluble orthophosphates and white precipitate with pyrophosphates and metaphosphates.

Magnesium sulphate gives a white precipitate with pyrophosphates,

soluble in excess of magnesium sulphate and not reprecipitated in the cold by ammonia. It does not precipitate metaphosphates in the presence of ammonium chloride.

Egg albumen is coagulated when shaken with metaphosphoric acid or with metaphosphates acidified with acetic acid. The ortho and meta acids are without action.

Phosphites are strong reducing agents. With silver nitrate a precipitate is produced which is momentarily white but which soon blackens. Mercuric salts are reduced to mercurous, and then to metallic mercury. When strongly heated, phosphites decompose, giving off phosphoretted hydrogen.

Hypophosphites are all soluble in water. They are even more powerful in their reducing action than phosphites. On adding copper sulphate to an acidulated solution of a hypophosphite and gently warming, a yellowish-brown precipitate is formed which quickly changes to chocolate-brown. This reaction distinguishes the hypophosphites from phosphites. When gently heated, hypophosphites evolve phosphoretted hydrogen.

The determination of the phosphoric acid radicle in soluble phosphates may be accomplished by the well-known method of precipitation with ammonium molybdate in presence of nitric acid and either titrating the precipitate or converting it to magnesium pyrophosphate.

If organic substances are present, the precipitation with molybdate is not complete. When this situation arises the sample should be diluted, made strongly ammoniacal and precipitated with magnesia mixture. The precipitate is recovered and washed free from mother liquor, dissolved in dilute nitric acid, and subjected to the molybdate precipitation. In some cases it may be desirable first to boil the sample with concentrated nitric acid, then dilute, precipitate with magnesia mixture, and proceed as above.

If the qualitative examination shows the presence of a pyrophosphate and it is desired to estimate the amount, the sample must be boiled with nitric acid before precipitating with molybdate. Mixtures containing pyrophosphates may contain organic matter, and after boiling with nitric acid, the solution should be treated with excess of ammonia, magnesia mixture added, and the well-washed precipitate dissolved in nitric acid and precipitated with molybdate.

In some instances the addition of ammonia to a complex mixture will cause a precipitate to appear before the magnesia mixture is introduced. But the subsequent solution of the precipitate in acid and precipitation with molybdate will eliminate any foreign substances.

Hypophosphites are readily determined by conversion to phosphates by oxidizing with nitric acid or permanganate. If by any chance soluble phosphates and hypophosphites occur together, the phosphate may be sep-

arated by throwing it out of ammoniacal solution with magnesia mixture.

Hypophosphites may be estimated by titration with permanganate. A dilute solution of the salt, free from organic matter, is acidified with dilute sulphuric acid, a slight excess of the reagent added and heated to 80 to 90° C., any red color remaining is removed by titration with oxalic acid. A further quantity of permanganate is then added and the same procedure repeated until the titration with oxalic acid shows that oxidation is complete.

The determination of phosphoric acid in glycerophosphates is accomplished by boiling under a reflux a solution of the sample with sulphuric acid and potassium bichromate for two hours. At the end of this period the hot mixture is diluted with water, the excess of bichromate reduced with sodium sulphite, and after the addition of sodium acetate, the phosphate precipitated with molybdate in presence of nitric acid. This procedure may be modified by neutralizing with ammonia after reducing the bichromate and making a preliminary precipitation with magnesia mixture, as was recommended in the assay of complex mixtures containing phosphates.

CARBON AND CARBONIC ACID

Wood charcoal is often present in remedies for certain forms of dyspepsia. It is dispensed alone with sugar and methyl salicylate, and in combination with mercurous iodide, with bismuth subnitrate, with magnesium oxide, with Nux Vomica, and often pepsin, Capsicum, and ginger are included in the formula.

The identification of carbon is a simple matter, because it is the only black substance which will withstand the action of chlorin even at high temperature. When burned in the presence of air or oxygen, the only product of combustion is carbon dioxide.

Wood charcoal may be determined with sufficient accuracy by dissolving out the other components of the tablet or lozenge with water, boiling the residual insoluble material with strong hydrochloric acid or chlorin water, diluting and filtering onto a Gooch. In case the insoluble mixture contains resistant siliceous matter, the carbon may be estimated by ignition in the organic combustion apparatus and the resulting carbon dioxide collected and weighed in the potash bulb.

Sodium bicarbonate is used in combination with a large number of different drugs, and in granular effervescent preparations and artificial mineral water salts. The normal carbonates are ingredients of many preparations, and the basic or subcarbonates of a few metals, notably

bismuth, are extensively employed. Lithium carbonate is used as a diuretic and antirheumatic.

Carbon dioxide, when dissolved in water, forms carbonic acid, H_2CO_3. The acid is capable of dissolving the normal carbonates of the alkaline earths and magnesium forming acid carbonates or bicarbonates. All normal carbonates are insoluble in water, except those of the alkalies. The acid or bicarbonates are all soluble, but on boiling their solutions they are converted into normal salts, which (except in the case of the alkali carbonates) are precipitated.

The normal carbonates of the alkalies are readily distinguished from the bicarbonates. A cold aqueous solution of the latter does not color phenolphthalein, but on warming, effervescence takes place, owing to the escape of carbon dioxide, and the solution acquires a deep-pink color.

These two classes of salts may also be distinguished by the difference in their behavior toward certain metallic solutions. With magnesium sulphate or chloride, normal alkali carbonates give a white precipitate of a basic carbonate,

$$5MgSO_4 + 5Na_2CO_3 = MgO \cdot 4MgCO_3 + 5Na_2SO_4 + CO_2$$

Sodium bicarbonate gives no precipitate with magnesium salts, the carbon dioxide being in sufficient quantity to redissolve the magnesium carbonate, forming magnesium bicarbonate.

With mercuric chloride the normal carbonates give a reddish precipitate of a basic oxide, while the bicarbonate gives no precipitate.

When strongly heated the normal carbonates of the alkali metals (not ammonium) remain unchanged. Those of the alkaline earths and other metals are converted into oxides with evolution of carbon dioxide.

The presence of a carbonate is determined by the evolution of carbon dioxide when the substance is treated with dilute hydrochloric acid, the gas being identified by its action on lime or barytes water. Sulphur dioxide which also produces a white precipitate with these reagents is distinguished by its characteristic odor, but if the two gases are liberated together both may be identified by passing the mixture first through a solution of potassium permanganate, which will absorb the sulphur dioxide, and then into lime water. If the passage of the gases through the permanganate be continued for a few minutes the color of the solution is entirely destroyed, and the liquid may then be tested for sulphuric acid by barium chloride.

The determination of the CO_3 radicle is seldom a matter of moment except in the cases of the alkali salts. In most of the other cases, after establishing the identity of the salt, the analysis proceeds to a determination of the metallic element, and from this datum the percentage of salt is calculated. A consideration of the procedures to be adopted when

working with ammonium carbonate and ferrous carbonate is discussed under the heading of these individual compounds.

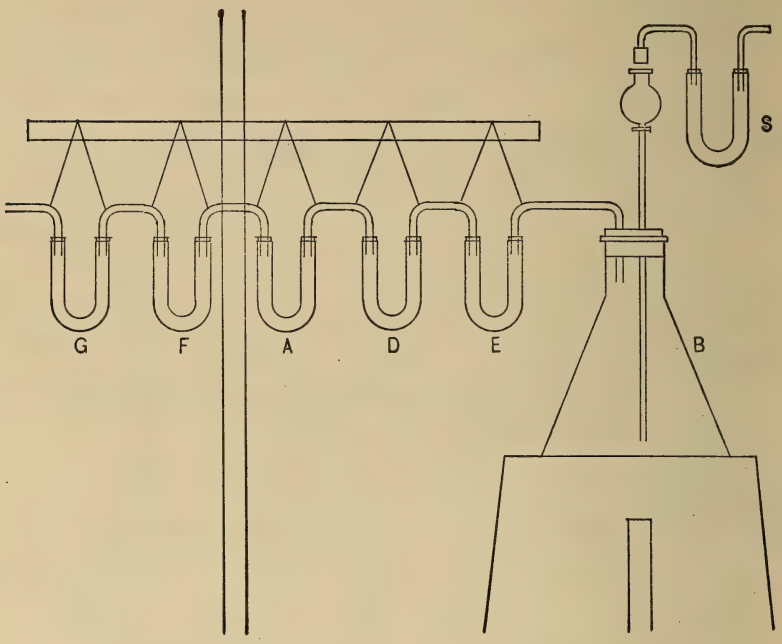
The purity of an alkaline carbonate is determined by dissolving a weighed amount of the same in water and titrating with standard acid. The following table gives size of sample and amount of acid required for neutralization if the assay is conducted according to the U. S. P. recommendations.

	Sample	H_2O	Acid	Alkali
Ammonium Carbonate.....	2 grams	50 mils	50 mils N/1 H_2SO_4 boiled	Not more than 12.7 mils N/KOH, Indicator litmus.
Lithium Carbonate.....	0.5 gram		20 mils N/1 H_2SO_4	Not more than 6.6 mils N/KOH. Indicator methyl orange.
Potassium Carbonate dried at 130°.....	1 gram	50 mils	Not less than 14.3 mils N/1 H_2SO_4	Indicator methyl orange
Sodium Carbonate.....	1 gram $Na_2CO_3 \cdot H_2O$ .855 gram Na_2CO_5	10 mils	Not less than 32.3 mils N/1 H_2SO_4	Methyl orange
Magnesium Carbonate recently ignited and cooled.....	0.4 gram		25 mils N/1 H_2SO_4	Not more than 5.8 mils N/1 KOH. Methyl orange.

The total carbonate in a granular effervescent salt is determined by treating the sample with dilute sulphuric acid and aspirating the evolved CO_2 into tared potash bulbs or tubes of soda lime.

Tube *E* contains pumice moistened with sulphuric acid, tube *D* contains pumice impregnated with anhydrous copper sulphate (prepared by soaking in strong copper sulphate solution and drying at 200° C.) and serves the purpose of absorbing acid vapors, tube *A* is filled about four-fifths with soda lime the remaining portion *a*, furthest removed from the incoming gas, being filled with dry calcium chloride. *F* is a guard tube of soda lime, *G* is a tube containing sufficient concentrated sulphuric acid to cover the bend, *S* contains soda lime for removing CO_2 from the air during aspiration.

The sample amounting to one to two grams is weighed into *B*, the stopper covering the funnel with 25–50 mils dilute sulphuric acid is inserted, and the apparatus connected, the absorption tubes *A* and *F* having been previously weighed. The acid is allowed to enter the flask slowly, the rate regulated by the escape of bubbles through tube *G*, which should not be faster than two per second. When effervescence is at an end the remainder of the acid is admitted, the stopcock left open, tube *S* attached and a slow stream of air aspirated through the system, gentle heat being applied to *B*. The aspiration should be continued for twenty to thirty minutes.



When the process is completed, the aspiration is stopped, the absorption tubes disconnected, the ends stoppered, cooled, and weighed.

The same apparatus and procedure can be used for determining the carbonates of the heavier metals used for excipients, etc., in other classes of medicinal preparations. Hydrochloric acid should be substituted for sulphuric.

SILICON AND SILICATES

Insoluble silicates find their way into medicinal products chiefly as excipients. Their exact determination is seldom a matter of moment unless one is concerned with working out a formula to its ultimate compo-

sition. In working with pills, tablets, and tooth powders it is usually sufficient to boil out everything that will dissolve in aqua regia, and then ignite the insoluble portion, and weigh the residue as siliceous matter.

A complete analysis of an insoluble silicate is conducted as follows:

From 1.5 to 3 grams of the silicate (which has been reduced to the finest possible powder, and dried) are weighed out into a platinum crucible of fairly large dimensions, and intimately mixed with five or six times its weight of fusion mixture, $(10Na_2CO_3 - 13K_2CO_3)$ by means of a stout platinum wire, or a thin glass rod with carefully rounded ends. The entire mixture should not more than half fill the crucible. The covered crucible is then heated over a Bunsen flame, at first gently in order to expel the moisture present in the mixture, and afterward more strongly until the mass begins to melt round the edges. It is then heated by means of a blowpipe, until the decomposition is complete and the contents of the crucible are in a state of quiet fusion. Care must be taken, by regulating the heat of the blowpipe, to prevent undue frothing of the mass while the carbon dioxide is being evolved; the progress of the operation should be watched by momentarily slightly raising the crucible lid from time to time.

When the operation is complete, the crucible is allowed to cool down, and when cold it is placed upon its side in a beaker with about 100 mils of water, care being taken that no impurities are conveyed into the solution upon the outside of the crucible. The beaker is heated upon an iron plate or sand-bath, and the water allowed to boil gently until the " melt " is either entirely detached from the crucible or has become honeycombed by the action of the hot water. Hydrochloric acid is then cautiously added in small portions at a time (the clock-glass cover being partially withdrawn for each addition) until effervescence ceases, and no further precipitaion of gelatinous silicic acid takes place. The crucible and lid are then withdrawn and rinsed into the beaker.

The mixture is transferred to a dish, and evaporated to dryness upon a steam-bath, the gelatinous mass, as it stiffens, being stirred at frequent intervals with a short glass rod, in order to break it up as much as possible and thus expedite the drying. When the mass has become white and pulverulent, the dish is transferred to an air-bath, and heated to about 160° for half an hour.

The residue is then moistened with a little strong hydrochloric acid, and digested upon the steam-bath for a short time, acid being added as evaporation goes on. Hot water is added, and the silica washed several times by decantation with hot water, after which it is transferred to the filter and washed until the wash-water is free from chlorides.

The silica is dried in the steam-oven, transferred to a platinum crucible, and the paper incinerated upon a platinum spiral. The covered

crucible is heated, at first very cautiously with a small flame, and afterward to a red heat, and weighed until constant.

Aluminum silicate forms the base of a class of soothing antiphlogistine preparations popular as applications for wounds, and swellings and as substitutes for poultices. These products are usually sold under fanciful names suggestive of their antiphlogistic properties and consist of the base with glycerin, boric acid, menthol, thymol, eucalyptol and ammonium iodide. Cataplasm of kaolin of the U. S. P. is a type of this class of products and contains 57.7 per cent kaolin.

BORON AND BORATES

Boric acid and sodium tetraborate are important medicinal agents. The latter is found in antiseptic dusting powders, gauzes, and washes; in soothing emollient preparations with glycerin, extract of witch hazel and Irish moss, as an excipient or lubricant in pills and tablets, and as an active ingredient of certain formulas used in cystitis, leucorrhea, and for gargles. It is found in eye washes, in liquids of the listerine type, and in ointments and salves combined with menthol, thymol, camphor, etc.

Sodium tetraborate or borax is a constituent of many alkaline antiseptic tablets, washes, and gargles; it is combined with potassium chlorate, cocain hydrochloride, resorcin, etc., and will be found in cystitis mixtures. It has been used as a remedy for epilepsy.

Sodium perborate, $NaBO_3+4H_2O$, is an antiseptic, deodorant, and bactericide, and liberates active oxygen when treated with dilute acids or water. It is used in the treatment of wounds, sores, ulcers, and disagreeable discharges, and is a component of certain classes of dentifrices, and so-called " peroxide " cold creams.

Zinc borate and perborate are used in dusting powders for wounds and eczema, as are also calcium borate and magnesium borate, the latter known as " Antifugin."

Boric acid is an ingredient of the antiphlogistic pastes popularly sold as applications for wounds and bruises following the formula of cataplasm of kaolin of the U. S. P.

Determination of Boric Acid.—*Boric Acid alone and in Talcum Powders Free from Carbonates.*—The sample is treated with water, an equal volume of glycerin added and titrated with sodium hydroxide using phenolphthalein.

In the U. S. P. assay for boric acid, if 1 gram is dissolved in 50 mils of water, 50 mils of glycerin added, not less than 16.2 mils N/1 sodium hydroxide should be required for neutralization.

Boric Acid or Borates in Presence of Carbonates.—The sample is treated with standard acid until the solution reacts acid to methyl orange. It

is then boiled under a reflux until carbon dioxide is expelled, cooled, neutralized to methyl orange, an equal volume of neutral glycerin added, and titrated with standard alkali using phenolphthalein.

Borates insoluble in water are dissolved in dilute hydrochloric acid in the cold or under a reflux, and treated as above.

Boric Acid and Borates in the Presence of Aluminum and Iron.—The sample is dissolved in hydrochloric acid and heated under a reflux until carbon dioxide is expelled. The mixture is cooled and made up to volume, an aliquot filtered off, nearly neutralized to methyl orange, barium carbonate added, warmed on steam-bath for half an hour, cooled, filtered, the filtrate treated with an equal volume of glycerin, and titrated as above.

Boric Acid and Borates in Salves and Ointments.—Five grams of the sample are treated with 30 mils of neutral glycerin and 50 mils of water and warmed on the steam-bath until the ointment is melted. The aqueous liquid is then treated as usual.

Another procedure is to dissolve the fats and oils in petroleum ether and wash the mixture with water. After separating, the ethereal layer is washed again with water and the combined aqueous solutions titrated.

Separation of Boric Acid from Other Substances, as Methyl Borate.—The following procedure is described by M. F. Schaak:[1]

The apparatus for distillation may conveniently be arranged as follows: A long wide-necked 200-mil Kjeldahl flask may serve as the decomposing flask. This flask is fitted with a stopper carrying three tubes, one of which serves to connect it with a condenser in such a manner as to avoid any of the acid liquid being carried over during the distillation. Another tube is to be connected with a flask for supplying a current of methyl alcohol vapor which is to be conducted to the bottom of the decomposing flask, thus serving to keep the mixture agitated and avoid bumping during the distillation. The third tube serves to introduce the methyl alcohol needed to form the mixture with the sulphuric acid and the substance, and may also be fitted with a clamp and valve for equalizing the pressure when needed. The receiver which is a tube connected with the condenser is trapped with a Mohr's bulb.

For the estimation a portion of the dry, finely pulverized substance is placed into a long, narrow tube and weighed. The contents are then emptied into the decomposing flask, without allowing any of the substance to remain in the neck of the flask. The tube is now weighed again, the difference being the amount of substance used for the estimation.

A sufficient amount of concentrated sulphuric acid is added to form a thin paste with the substance, and the flask heated gently to expel carbon dioxide or other volatile acid, and cooled.

About 60 mils of water are placed in the receiver, the terminal tube

[1] J. Soc. Chem. Ind., 1904, 23, 700.

of the condenser being made to dip into the water. The Mohr's bulb is also filled with water and attached as a trap to the receiver. The decomposing flask, containing the cold mixture of the substance and sulphuric acid, is now connected with the flask for the generation of methyl alcohol vapor, and with the condenser, all the connections being air-tight.

The distillation is then started by adding to the decomposing flask, in one portion, sufficient cold methyl alcohol to equal about 20 times the amount of free sulphuric acid present. Methyl alcohol vapors are then passed from the generating flask until the boric acid has all passed into the receiver.

During the distillation the decomposing flask is heated to a temperature sufficient to prevent any marked change of volume of the methyl alcohol which was originally added.

The distillation will usually be complete in about thirty minutes, when the receiver can be changed, and, to ensure complete removal of the boric acid from the substance, a further distillate collected and tested.

The water from the Mohr's bulb is added to the distillate, which is then neutralized with alkali, when necessary, by the aid of Congo-red or methyl orange test-paper. The titration is then completed after the addition of neutral glycerol and phenolphthalein.

When pure methyl alcohol is used and care is taken not to allow the mixture with sulphuric acid in the decomposing flask to become concentrated, accurate results can be attained, even in the presence of large amounts of chlorides and carbonates. Fluorine, when present in large amount, must be removed from the substance before distillation.

PERBORATES

The perborates have assumed considerable prominence during recent years because of the ease and rapidity by which hydrogen peroxide is evolved when they are treated with water or dilute acids. Certain salts of other acids containing a large amount of oxygen have been placed on the market and the analyst will be confronted with the problem of deciding which particular substance has been used in compounding a mixture. Lenz and Richter [1] have studied the reactions of a number of these substances toward certain reagents. They compare the behavior of (*a*) sodium perborate, (*b*) potassium percarbonate, (*c*) ammonium persulphate, (*d*) potassium perchlorate, and (*e*) periodic acid; *a* and *b* are decomposed by water with the formation of hydrogen peroxide and liberation of oxygen; *c* gives oxygen only. Permanganate solution in the presence of sulphuric acid is decolorized by *a* and *b* and by *c* slightly on heating; *d* and *e* have no effect; alkaline permanganate is turned blue by *d*. With

[1] Znal. Chem., 1911, 50, 537.

silver nitrate solution a heavy black precipitate is produced by *a* (a mirror on warming in the presence of ammonia); a white precipitate turning gray on warming, with *b*; a solution of *c* becomes turbid through the separation of blue molecular silver; *d* has no action; *e* gives a pale-yellow precipitate readily soluble in ammonia. *a*, *b*, *c*, and *e* cause the darkening of freshly precipitated manganous hydroxide (in absence of air); *d* has no effect. The precipitate obtained by adding sodium hydroxide to cobalt nitrate, in absence of air (under petroleum ether) is darkened at once by *a*, *b*, and *c*, but not by *d* and *e*. When nickel sulphate is treated similarly, a black precipitate is given by *c*; the others have no effect. Alkaline lead acetate solution, when heated with an excess of *c*, gives a yellow-red precipitate after a time; with *e* a heavy white crystalline precipitate is obtained; *a*, *b*, and *d* have no effect. Cerous chloride solution, in the presence of ammonia, is colored yellow by *a* and *b*; the others have no effect. Iodin is liberated from potassium iodide by *c*, and in the presence of sulphuric acid by *a* and *b*; *d* has no effect. Fuchsin solution, containing sodium acetate, is decolorized by *a*, *b*, and *c* on warming, but not by *d*. Anilin sulphate solution is colored a pale yellow when heated with *a* or *b*; *c* gives a dark-brown precipitate and *d* has no action.

E. K. Farrar [1] has proposed the following method for the estimation of perborates. A known weight of the sample in the solid condition is added to an excess of ferrous ammonium sulphate in water which has been acidulated with sulphuric acid. Potassium thiocyanate is added as an indicator, and the ferric iron titrated with a standard solution of titanous chloride. An alternative method consists in adding the sample to a measured volume of titanous chloride solution which must be in excess (the operation being performed in an atmosphere of CO_2) and titrating the excess of titanous chloride with iron alum, using potassium thiocyanate as indicator.

Estimation of Perborates in Soap Mixtures, Creams, etc.—The sample is weighed into a glass-stoppered volumetric flask, water added, warmed to 50 to 60° and shaken for five minutes. Dilute sulphuric acid is added in excess, followed by 1 gram ignited kieselguhr, the solution made up to volume and allowed to settle. Aliquots are then filtered off and titrated with permanganate.

[1] J. Soc. Dyers and Col., 1910, 26, 81.

CHAPTER XXVI

METALS AND THEIR COMPOUNDS

SILVER

Silver compounds are important therapeutic agents. They functionate as antiseptics and bactericides, and in some forms are introduced directly into the blood stream. Silver salts are also employed as alteratives, stimulants, and nerve sedatives, and preparations containing them will be found recommended for a wide range of ailments, including epilepsy, locomotor ataxia, typhoid fever, chronic diarrhea, gastric troubles, etc. They find their widest use in gynecological practice, and on account of the demand for non-irritant agents, there have sprung up a quantity of organic silver compounds of indefinite composition. Of late silver salts have been exploited as cures for the tobacco habit.

The salts used as medicaments include the nitrate, acetate, arsenite, chloride, citrate, cyanide, iodate, iodide, lactate, and sulphocarbolate. The oxide, mixed with chalk, is dispensed in capsules. The organic combinations are chiefly of a proteid nature, and will be discussed individually.

Silver nitrate is recognized in the U. S. P. Molded silver nitrate or lunar caustic is the crystalline salt with 4 per cent hydrochloric acid. Mitigated silver nitrate U. S. P. contains $33\frac{1}{3}$ per cent of the crystalline salt, with the balance potassium nitrate. It is sometimes called mitigated lunar caustic No. 4. Two other mixtures of these two salts are marketed, one containing 67 per cent and the other 50 per cent $AgNO_3$, and known respectively as mitigated lunar caustic No. 2 and No. 3. These remedies are used in the treatment of the diseases above mentioned, and are locally applied in gonorrhea, conjunctivitis, cystitis, stricture, excrescences, warts, ulcers, hemorrhoids, chancre, diphtheria, hydrocele, smallpox, etc.

Silver cyanide and oxide are both recognized in the U. S. P. Silver in inorganic combinations is readily recognized when conducting the regular scheme of qualitative analysis, but when in organic combinations and under certain conditions in the presence of organic acids, it does not respond to the analytical reagents. When the latter condition prevails the organic matter must be destroyed by digestion with nitric and sulphuric acid before the identification tests can be applied.

For assaying silver nitrate crystals, molded silver nitrate and mitigated

silver nitrate, the pharmacopœial procedure consists in dissolving the salt in 10 mils of water, adding a certain quantity of sodium chloride standard solution and then titrating back with a certain limited amount of silver nitrate.

	Amt. used	N/10 NaCl	N/10 $AgNO_3$	Indicator
Silver Nitrate.....	0.5 gram	30 mils	0.4 mil	3 drops K_2CrO_4
Molded silver nitrate....	0.5 gram	30 mils	1.9 mils	3 drops K_2CrO_4
Mitigated silver nitrate..	1.0 gram	20 mils	0.3 mil	3 drops K_2CrO_4

In assaying silver cyanide, the salt is fused in a porcelain crucible, and after ignition, should leave a residue of metallic silver amounting to 80.48 per cent of its original weight.

No better method for estimating silver exists than precipitating a solution of the salt with dilute hydrochloric acid in presence of nitric acid, and weighing the silver chloride on a Gooch.

If the sample in hand consists entirely of inorganic material, and the silver salt is soluble in water, and there are no other metals present precipitated by hydrochloric acid, a weighed amount is diluted with water to about 100 to 200 mils, filtered if necessary from any insoluble residue, 5 to 10 mils dilute nitric acid added, heated to boiling, and dilute hydrochloric added until the precipitate coagulates and settles out, leaving the supernatant liquid clear when the flame is withdrawn. If the addition of a few drops of hydrochloric acid shows that the precipitation is complete, the silver chloride is collected on a tared Gooch, washed with water, rinsed with alcohol and ether, and dried at 100°.

$$AgCl : Ag = 1 : 0{\cdot}75202$$

If the sample contains a halogen salt of silver, the metal may be obtained in a solution by fusing in a porcelain crucible, adding water, followed by a piece of pure zinc and some dilute sulphuric acid. The reduced spongy silver is afterward washed with dilute sulphuric acid and water, and then dissolved in nitric acid.

If the sample consists of a colloidal suspension of silver oxide or an organic mixture, a weighed quantity is either evaporated or treated with 10 to 15 mils concentrated sulphuric acid in a porcelain evaporating dish, and heated until well charred. After cooling, nitric acid is added, heated, and if the liquid does not char again after the nitrous fumes have all boiled away, it is cooled, diluted with water, and precipitated with hydrochloric acid, as above. Should lead or mercuric mercury be present simultaneously with silver a small quantity of sodium acetate should be added to insure the complete precipitation of the silver chloride.

In some cases it will be sufficient to ignite the substance in a porcelain crucible and weigh the resulting silver. Igniting should be gentle at first afterward with the full flame. If the substance leaves a residue which appears to contain silver chloride or a halogen salt, it is converted to metallic silver with zinc and sulphuric acid, and the determination completed by dissolving in nitric acid and precipitating with hydrochloric acid.

COLLOIDAL SILVER

Under certain conditions silver in a very fine state of subdivision forms a colloidal suspension which gives with water a mixture closely resembling a solution. Colloidal silver is not precipitated by the ordinary reagents which precipitate the metal from solution, thus sodium chloride or albumen are without effect, but if the suspension is first warmed with nitric acid until the silver is dissolved, the resulting solution will respond to the usual silver tests. Colloidal silver is used for the preparation of ointments, dusting powders, vaginal tampons, suppositories, and tablets.

Among the colloidal preparations on the market may be mentioned, Cargentos, Collargol, and Electrargol.

Cargentos is said to be prepared by precipitating an alkaline solution of silver caseinate and silver oxide with an acid, dissolving the precipitate in an alkali, dialyzing the resulting solution against running water and evaporating the remaining colloidal suspension to dryness *in vacuo*. It occurs in odorless and tasteless black scales of metallic luster, which form colloidal suspensions with water and glycerin. It contains from 48 to 52 per cent metallic silver.

Collargol occurs in hard, brittle, bluish-black, scale-like pieces, forming with water a dark olive-brown colloidal suspension.

Electrargol is a colloidal suspension of silver containing a small percentage of sodium arabate. It contains silver equivalent to .25 per cent. It is prepared by passing an electric current in the form of an arc between two silver electrodes in distilled water. It is made stable by the addition of sodium arabate. The liquid is odorless and tasteless, appearing transparent by transmitted light and opaque and gray by reflected light.

SILVER COMPOUNDS WITH PROTEIN SUBSTANCES

Albargin.—Gelatosesilver

Albargin is a compound of silver nitrate with gelatose, containing from 13 to 15 per cent of silver.

It is prepared by adding silver nitrate to a solution of gelatose in water, evaporating the solution or precipitating the compound by the addition of ether or alcohol. It is a coarse, yellow, shining powder, very easily

soluble in water, forming neutral solutions. The presence of gelatose, silver, and a nitrate can be shown by appropriate tests. It is incompatible with tannin and chlorides.

Argonin.—Caseinsilver—Silvercasein

Argonin is a compound of silver and casein containing 4.28 per cent of silver.

It is prepared by precipitating an alkaline solution of casein with silver nitrate and alcohol. It is a fine, nearly white powder, easily soluble in water, forming an opalescent, faintly alkaline solution, which becomes clear on the addition of sodium chloride. It is also soluble in alkaline solutions, in egg albumen, blood serum, etc.

The usual reagents for silver do not affect its aqueous solution (1 in 20), which should remain clear on addition of sodium chloride, and should not be affected by hydrogen sulphide. On incineration argonin should yield at least 4 per cent of silver, which may be identified by the usual tests after solution in dilute nitric acid, It is incompatible with acids.

Argyrol.—Silver Vitellin

Argyrol is a compound of a derived proteid and silver oxide, containing from 20 to 25 per cent of silver.

The so-called vitellin is said to be prepared by electrolytic decomposition of serum albumin. To this product, finely suspended in water, is added freshly precipitated, moist silver oxide and the mixture is heated under pressure until combination occurs. The liquid is then evaporated to dryness *in vacuo*. The change in the proteid is in question; probably a compound of hydrolyzed proteid (serum albumin) and silver oxide is formed.

Argyrol occurs in black, glistening, hygroscopic scales. The solution is yellowish or black, depending on concentration, and is not affected by boiling. Solutions of argyrol stain the skin. It gives a slight cloudiness or precipitate with sodium chloride and hydrochloric acid; on addition of ferric chloride the color is discharged with formation of a white cloud. With alkali and copper sulphate it gives a slight biuret reaction. It has a slight metallic taste. Silver is recognized in the usual way.

The compound is said to be incompatible with acids and most of the neutral and acid salts in strong solution.

Hegonon.—Silver Nitrate Ammonia Albumose

Hegonon is a substance obtained by treating silver ammonium nitrate with albumose, said to contain approximately 7 per cent of organically combined silver.

It is a light-brown powder readily soluble in water. Its aqueous solutions do not coagulate albumin, even on heating, nor are they precipitated by sodium chloride.

Novargan.—Silver Proteinate

Novargan is an organic silver-albumin compound containing 10 per cent of silver.

It is a fine yellow powder, soluble in water, forming a practically neutral solution, from which it is not precipitated by sodium chloride, nor affected by the usual reagents for silver salts.

The solution is darkened by hydrogen sulphide or ammonium sulphide, but no precipitate is produced.

Protargol.—Protein Silver Salt

Protargol is a compound of albumin and silver, containing 8.3 per cent of silver in organic combination.

According to the patent specifications insoluble protein silver compounds, obtained by treating protein bodies with silver salt, are rendered soluble by treatment with a solution of albumoses.

It is a light-brown powder, soluble in twice its weight of cold water, producing a solution which is not affected by the ordinary precipitants of silver salts, such as alkalies, sulphides, chlorides, bromides, iodides, nor by heat.

Ammonium sulphide gives a dark color to the solution without precipitation. Addition of strong hydrochloric acid produces a precipitate of unchanged protargol, soluble in a large quantity of water. A solution containing sulphuric acid is not colored blue by diphenylamine. It is compatible with picric acid and picrates and with most metallic salts.

Sophol

Sophol is a compound of silver and methylene-nucleinic acid, containing about 20 per cent metallic silver. It is prepared by corrosion of insoluble silver compounds of methylene-nucleinic acid into soluble silver compounds by treatment with neutral salts, such as sodium chloride. It is a yellowish powder, readily soluble in water, insoluble in alcohol or ether. The aqueous solution has a faint alkaline reaction and is not precipitated by dilute sodium hydroxide or by sodium chloride. When boiled with dilute alkali it assumes a black color and the odor of formaldehyde is apparent. An aqueous solution yields a yellowish precipitate on warming with nitric acid; the precipitate is soluble in ammonia, the solution becoming orange.

Nargol

Nargol is a compound of silver and nucleinic acid and contains about 10 per cent of metallic silver.

Largin

Largin is a protein compound of silver containing 11 per cent of the metal. It is a gray powder, soluble in water and glycerin.

Argentamin.—Ethylene-Diamine-Silver Nitrate

Argentamin is an aqueous solution of silver nitrate and ethylene-diamine, corresponding to 10 per cent of silver nitrate.

It is prepared by dissolving 10 parts each of silver nitrate and ethylene-diamine in 100 parts of water. It is a colorless, alkaline liquid, turning yellow on exposure to the light, but not precipitable by chlorides or albumin.

LEAD

Lead acetate is astringent and sedative and will be found in pills and tablets combined with opium and camphor, and in astringent washes with Hydrastis alkaloids, zinc salts, and morphin. It is a component of liquid hair dyes when it occurs with suspended sulphur. Its solution is also used as an astringent eye lotion and as an injection and wash for gonorrhea. The subacetate is employed in solution, the 25 per cent strength being known as Goulard's extract and the 1 per cent solution being official. It is employed externally for burns, bruises, sprains, blisters, inflamed conditions of the eyes, ivy poison, erysipelas, and as an injection for gonorrhea.

Lead sub-carbonate, $2PbCO_3 \cdot Pb(OH)_2$, is used as a dusting powder for burns, and occurs in ointments for ulcers, carbuncles, and skin diseases. It will be found in cosmetics, powders and creams.

Lead nitrate is employed in a limited way for the same purposes as the acetate. Lead monoxid, PbO, the yellow oxide or litharge, is one of the forms in which lead is exhibited in ointments. The sulphite is used as a local application for erysipelas, scabies, and various skin affections. The tannate is used for the same purposes.

Lead oleate is the lead compound present in lead plasters. It is soluble in alcohol, ether, and oil of turpentine. This compound is the basis of certain types of proprietary ointments recommended for raw sores and infections, bites of animals, wounds, etc., where it is combined with Peru or Tolu balsams.

Lead sulphocarbolate is a crystalline salt soluble in water and alcohol. The diiodophenolsulphonate is known as Sozoiodole-lead, and is slightly soluble in cold water, and dissolves readily in presence of acetic acid.

The identification of lead when present in inorganic combinations and in most of the organic compounds, will result when the regular scheme of analysis is followed. If one is working with a plaster or a stiff ointment, lead oleate will dissolve in ether, and on shaking with dilute sulphuric acid, insoluble lead sulphate is formed, which can be filtered out from the acid solution and identified by appropriate means.

Lead is determined by conversion to the sulphate or sulphide. If the sample contains lead acetate or nitrate in solution in water, or capable of solution in water free from organic matter a weighed amount is filtered from any insoluble matter, and treated with an excess of moderately dilute sulphuric acid and double the volume of ethyl alcohol. After standing a few hours, the precipitate is collected on a tared ignited Gooch, washed with water, and alcohol, dried and ignited. If the solution contains nitric acid or a nitrate, it is advisable to evaporate on the steam-bath after the addition of the sulphuric acid until all of the nitric acid is expelled. The residue is then diluted, alcohol added and the remainder of the determination conducted as above described.

If the sample is a powder and contains lead carbonate or oxide, the lead is brought into solution by treatment with nitric acid. Should calcium salts be present simultaneously with lead, the precipitation with sulphuric acid cannot be followed, and resort must be had to the sulphide determination.

Ointments containing inorganic lead salts are first treated with ether to dissolve the fatty base, and the insoluble lead salts brought into solution with nitric acid.

Lead plasters or ointments containing lead oleate may be dissolved in ether, transferred to a separatory funnel, and shaken with dilute sulphuric acid. The acid layer containing the lead sulphate is conducted into a flask, and the ethereal layer repeatedly shaken, if necessary, with the acid until no further precipitate takes place. The combined acid mixtures are then treated with twice the volume of alcohol and the remainder of the determination conducted as above.

If the plaster or ointment contains no other inorganic salt, the following procedure may be used:

Determination of Lead in Mixed Galenicals.—If it is desired to determine the lead in the whole plaster including the gauze, weigh out a sample of about 5 to 10 grams and place it in a tared porcelain evaporating dish of about 100 mils.

If it is desired to determine the lead as the medicament alone, the plaster must be weighed then treated with ether in a porcelain dish large enough to hold the plaster spread out and the ethereal extract should be carefully transferred to the tared evaporating dish in which the subsequent digestion is to be made, and the solvent evaporated on the steam-

bath. After three or four washings and gauze will be free from the lead salt and may be dried and weighed, the difference in the weighing representing the medicament.

Cover the material in the evaporating dish with 100 mils of concentrated sulphuric acid and heat over the steam-bath. Watch carefully and remove from the bath if there is violent frothing. When the mixture is thoroughly charred transfer to an asbestos plate and heat gently for an hour or more until SO_3 fumes cease to be evolved. Cool. Add 5 mils fuming nitric acid and allow to digest until violent reaction is over. Add 5 mils concentrated sulphuric acid and heat gently as before and remove flame if reaction becomes violent. After the last fumes of SO_3 have been driven off, place the evaporating dish over the free flame and heat at a low heat so that carbonaceous matter will ignite slowly.

If there still remains any quantity of resistant carbonaceous material, allow the dish to cool, add 5 mils fuming nitric acid and allow to digest overnight. Evaporate off excess of acid on steam-bath, add 5 mils concentrated sulphuric acid. Heat gently over asbestos plate as before and finally ignite at low redness. This last treatment with nitric acid and sulphuric acid will generally yield a white residue. Cool and weigh as lead sulphate.

NOTE.—To obtain an even heat and prevent spurting when evaporated over asbestos plate, place a pipestem triangle on the asbestos and the evaporating dish on this.

When soluble lead salts occur in pills or tablets with organic matter which will yield a precipitate with lead, the sample should be well ground, triturated with water, and the aqueous liquid filtered. The residue is then triturated with 5 per cent potassium hydroxide which is poured into the filter, the alkaline liquor collected, and added to the aqueous solution. The solution is then subjected to a stream of hydrogen sulphide, and when precipitation is complete, the sulphide is collected on a tared Gooch, well washed with hot water, dried with alcohol, washed with freshly distilled carbon bisulphide, again washed with alcohol, dried at 100° and weighed.

If zinc or iron are known to be present, the combined sulphides are filtered, washed, and then treated with dilute hydrochloric acid before addition of alcohol and carbon bisulphide.

Assay of Goulard's Extract U. S. P.—Transfer about 1.5 gram, accurately weighed, to a 200-mil measuring flask, dilute with 50 mils recently boiled distilled water, then add 50 mils N/10 oxalic acid, agitate the mixture thoroughly for five minutes, fill to the mark with distilled water, and filter rejecting the first 20 mils of the filtrate. Add 5 mils of sulphuric acid to 100 mils of the filtrate (representing one-half the amount of solution originally taken), warm to about 70° and titrate with N/10 permanga-

nate. It shows not less than 18 per cent of lead. Each mil of N/10 oxalic used corresponds to .010355 gram of lead.

MERCURY

Mercury, its salts and organic compounds are important remedial agents.

Metallic mercury in confection of rose is known as Blue Mass, and is used as a cathartic and alterative. Mercury with chalk is used as an antiemetic and alterative, especially adapted for children. Blue mass is dispensed in pills and tablets by itself and in combination with ipecac and opium; with colocynth compound alone and combined with ipecac, Hyoscyamus, aloes, or rhubarb; with colocynth compound, ipecac, strychnin, and belladonna; with Podophyllum resin; with Nux Vomica, Hyoscyamus, Capsicum and Podophyllum resin; with aloes, jalap, and tartar emetic; with ipecac and Gelsemium; with quinin and black pepper oleoresin; with rhubarb and sodium bicarbonate; with aloes and Podophyllum resin; with Digitalis and squills; with aloes, scammony, croton oil, myrrh, and oil of caraway; with strychnin, ipecac, Capsicum, and gentian; with quinin, Colchicum, Hyoscyamus, and opium.

Mercury and chalk is dispensed alone in pills and tablet triturates. It is combined with gentian, ipecac, and opium; with gentian, Nux Vomica and reduced iron; with salol and bismuth subnitrate; with opium, camphor, bismuth subnitrate, kino and sodium bicarbonate.

Mercurial ointment consists of mercury in a fine state of subdivision, in a medium of suet and lard. Oleate of mercury is added in small amount in the preparation of the U. S. P. product. This preparation is used extensively to destroy parasitic infections, as a resolvent in glandular swellings, venereal disease, for smallpox, erysipelas, and chilblains. Compound mercurial ointment contains in addition to the regular formula, camphor, olive oil, and beeswax.

Oxides of Mercury

Red mercuric oxide or red precipitate, is used externally for chancres, ulcers, ringworm, and inflamed conditions of the eyes. The yellow oxide is employed in syphilis and in acute and chronic derangements of the alimentary tract, in typhoid fever, phthisis, and functional disturbance of the liver. These substances are administered chiefly in the form of ointments.

Black oxide of mercury is oxydimercurous ammonium nitrate, $Hg_2O+NH_2Hg_2NO_3$, and should not be confused with the true oxides of mercury.

Mercuric Salts

Mercuric chloride is employed as an antiseptic and germicide, both in professional and household practice. It is also used in syphilis, and externally as a stimulant and escharotic. Mercuric chloride pills and tablets are prepared in several different strengths from 1/1000 to 1/8 grain. Antiseptic tablets are composed of mercuric chloride with either ammonium chloride, sodium chloride, or citric acid, often colored red or blue. Antisyphilitic pills contain mercuric chloride and potassium iodide, sometimes with the addition of opium. Mercuric chloride is also combined with morphin and copper arsenite; with quinin, ferric chloride, and arsenic chloride; with potassium iodide, ferrous iodide, arsenic iodide, and Nux Vomica; with opium and guaiac. Mercuric chloride is used in the preparation of antiseptic bandages and surgical dressings.

Mercuric bromide is combined with the bromides of gold and arsenic in remedies for neurasthenic and anemic conditions.

Mercuric iodide, red iodide, is used in syphilis, rheumatic conditions due to venereal disorders and scrofula, and externally for lupus. Mercuric iodide is dispensed in pills and tablets alone and in combination with arsenic and ferrous iodides; with aconite, belladonna, and bryonia for tonsillitis; with morphin, sodium salicylate, and methyl salicylate. It is also used in the preparation of surgical soaps.

Mercuric cyanide is recommended in diphtheria, membranous croup, and syphilis. It is used in the form of a gargle and tampons.

Mercuric nitrate is used internally for syphilis and scrofula, and externally for removing freckles and absorbing boils.

Mercuric acetate, arsenate, benzoate, cacodylate, gallate, iodate, oxycyanide, phosphate, basic salicylate, carbolate, basic sulphate, are all used medicinally in limited amount.

Mercurous Salts

Mercurous chloride or calomel combines the general properties of mercurial salts with those of a purgative and anthelmintic. Calomel is prepared for administration in pills and tablets of different strengths. It is combined with sodium carbonate; with ipecac; with ipecac and opium; with Podophyllum resin and sodium bicarbonate; with bismuth subnitrate; with Capsicum; with santonin; with ipecac and bismuth subnitrate; with sulphurated antimony and guaiac, and castor oil (Antimony comp. U. S. P. Plummer pills); with colocynth compound; with opium; with rhubarb, colocynth compound, and Hyoscyamus; with colocynth compound, jalap, gamboge, Hyoscyamus, and oil of peppermint; with colocynth compound, jalap, ginger, gamboge, and rhubarb; with colocynth

compound, jalap, and gamboge (Cathartic Comp. U. S. P.); with aloes, rhubarb, and soap; with morphin, Capsicum, ipecac, and camphor; with Podophyllum resin, colocynth compound, belladonna, ipecac, Nux Vomica, and oil of anise; with aloes, jalap, gamboge, Veronica officinalis, Capsicum, Veratrum viride, and croton oil; with colocynth compound, Nux Vomica, aloes, Hyoscyamus, and ipecac; with colocynth compound, Colchicum, and Hyoscyamus; with Euonymus, ipecac, Podophyllum resin, and aloin; with zinc sulphocarbolate, salol, bismuth subnitrate and pancreatin; with atropin, morphin, and aconite; with quinin, ipecac, opium, aconite, aloin, and Capsicum.

Mercurous iodide (yellow iodide) is an antisyphilitic. It is dispensed in pills and tablets alone and in combination with opium; with charcoal; with Conium, Lactucarium, and opium; with Podophyllum resin, aloin, Hyoscyamus, and Nux Vomica.

Mercurous bromide is used as an alterative and antiseptic.

Ammoniated mercury, $HgNH_2Cl$, or white precipitate, is obtained by precipitating mercuric chloride with excess of ammonia. This salt is used externally in skin diseases, syphilitic sores and eruptions, and is often found in cosmetics. The term " white precipitate " (*precipité blanc*) is confusing, as it is used by the French as a term for designating calomel.

Mercury oleate, prepared from mercuric oxide and oleic acid, is one of the forms in which mercury is administered internally.

Mercuric succinimide is a salt of mercury and succinic acidimide. When suspended in ether and subjected to a stream of hydrogen sulphide, the mercury is precipitated as sulphide and the succinimide can be subsequently recovered from the ether.

Afridol

Afridol is sodium hydroxymercuric toluylate, $C_6H_3(CH_3)(COONa)HgOH$ 2 : 3 : 1. It is an odorless, tasteless white powder, difficultly soluble in neutral or acid media, but soluble in ammoniacal solution containing ammonium chloride. Filtered aqueous solutions of afridol remain unchanged on the addition of ammonium sulphide solution or albumin solutions.

If afridol is boiled with hydrochloric acid, an odor of benzoic acid is produced and the cooled solution when saturated with hydrogen sulphide yields a black precipitate of mercuric sulphide. This product is marketed in the form of a 4 per cent soap.

Mercurol.—Mercury Nucleinate

Mercurol is an organic compound of mercury with nucleinic acid from yeast, containing 10 per cent of metallic mercury. It is prepared by adding

a solution of mercuric chloride to an alkaline solution of nuclein, containing an excess of alkali, precipitating the resultant nucleinate of mercury by the addition of alcohol and a concentrated solution of a neutral salt (sodium chloride), separating the precipitate, washing and drying it.

It is a brownish-white powder, soluble in water, especially in warm water, insoluble in alcohol. Its watery solution has a distinct metallic taste, a weak alkaline reaction, and is not precipitated by alkalies, by albuminous liquids, nor hydrogen sulphide.

Mercurol does not coagulate albumin; it has marked bactericidal power and possesses the pharmacologic action of soluble mercury compounds.

It is recommended as a local antiseptic application and as an antisyphilitic remedy.

Sublamine.—Mercuric Sulphate Ethylenediamine

Sublamine, $HgSO_4 \cdot 2C_2H_4(NH_2)_2 + 2H_2O$, is a compound of one molecule of mercuric sulphate with two molecules of ethylenediamine. It forms white needles, readily soluble in water and in 10 parts of glycerin, sparingly soluble in alcohol. It has an alkaline reaction; it contains about 44 per cent of mercury. It does not precipitate albumin from its solutions.

Sublamine is a disinfectant. It is used as a substitute for mercuric chloride for hand disinfection, as well as in dermatology, gynecology, ophthalmology, and otology.

Electr-Hg.—Electromercurol

Electr-Hg is a colloidal suspension of mercury equivalent to .1 per cent metallic mercury and containing a small percentage of sodium arabate.

Electr-Hg is prepared by passing an electric current in the form of an arc between two mercury electrodes in distilled water. It is made stable by the addition of sodium arabate, which is prepared by acting on acacia (gum arabic) with hydrochloric acid, precipitating the resultant arabic acid with alcohol and neutralizing the arabic acid with sodium carbonate.

Electr-Hg is an odorless, tasteless liquid, appearing transparent and brown in color by transmitted light and opaque and gray by reflected light. The addition of potassium cyanide solution or of strong nitric acid yields clear, colorless solutions. The nitric acid solution responds to tests for mercury.

Electr-Hg is claimed to have an action similar to that of the soluble salts of mercury. Locally it is said to produce no pain when given by intramuscular injection, and to leave no induration.

Hyrgol is a colloidal form of mercury. It is a nearly black, substance, soluble in water and used for syphilis in the form of ointments and plasters.

Calomelol.—Colloidal Calomel

Calomelol is a colloidal form of calomel, containing albuminoids.

According to the patent, this drug is prepared by acting on a solution of sodium chloride in presence of a proteid with mercurous nitrate and precipitating the colloidal calomel by means of alcohol. The precipitate is washed with alcohol, redissolved in water with the aid of a little alkali, and from this solution the colloidal calomel is obtained either by evaporation or by precipitation with alcohol.

It forms a white-gray, odorless and tasteless powder, containing 80 per cent of mercurous chloride and 20 per cent of proteids. With water it forms an opalescent suspension insoluble in alcohol, ether, and benzene. It is precipitated from its aqueous suspension by acids, the precipitate being redissolved by alkalies.

Determination of Mercury.—The determination of mercury is accomplished by conversion to the sulphide and weighing, by depositing the metal electrolytically, or by iodin titration.

In 1911 the Committee on Quantitative methods of the Pharmaceutical Section of the American Chemical Society suggested the following method for assaying mercury salts, which is applicable to all the mercury compounds of the Pharmacopœia as well as to other simple salts of mercury.

Mercurous Chloride, Bromide and Iodide and Mercuric Iodide.—Weigh out accurately about .2 gram of the sample, dissolve in 20 mils water with the aid of 1 gram potassium iodide. Add 10 mils of 10 per cent sodium hydroxide followed by 3 mils of 40 per cent formaldehyde diluted to 10 mils with water. Warm on the water-bath for ten minutes or until complete precipitation of the mercury takes place, swirling the container occasionally. Decant through a Gooch filter, and wash the precipitated mercury thoroughly with water. Dissolve off the filter with 2 c.c or more concentrated nitric acid, washing the filter carefully with water.

From this point the process may be applied also to *Mercuric Oxide,* by solution in 2 c.c. concentrated nitric acid.

Metallic Mercury, Mercury with Chalk and Mercuric Nitrate.—Evaporate the solution to dryness on water-bath and take up with 2 mils concentrated hydrochloric acid and water sufficient to make 50 mils of solution.

From this point the process is applicable to *Mercuric Chloride* by solution as above. Precipitate the mercury from this solution in the cold by a slow stream of hydrogen sulphide, let settle and filter onto a tared Gooch. Wash thoroughly with water and three times with alcohol.

Wash with recently distilled carbon bisulphide to remove any adhering sulphur, then with alcohol and finally with ether. Dry at 100 to 110° and weigh. $HgS \times .8621 = Hg$.

When carefully conducted this method gives good results and it is applicable to almost any pill or tablet containing salts of mercury.

B. L. Murray proposes the following electrolytic procedures for assaying mercury compounds.

If the mercury preparations of the U. S. P. are first converted into mercuric nitrate they are then readily subjected to electrolysis to determine the per cent of mercury. This is practical with mercury oxide red, mercury oxide yellow, metallic mercury, and with mercury with chalk. Solution of mercuric nitrate U. S. P. may also be assayed for the mercury present after proper dilution to bring it to the usual concentration. The general statement of the method is to dissolve about 0.5 gram sample in about 1 mil of nitric acid (sp. gr. 1.20), dilute to about 20 mils and subject the solution to electrolysis. Use the mercury cathode and the rotating anode, the latter revolving about 700 to 800 times per minute. The voltage should be 10 to 12, the amperage 3, and fifteen minutes at room temperature will be found sufficient time for the electrolysis to become complete. The mercury cathode is then washed with water, alcohol, and ether in the usual way, any increase in weight being due to the metallic mercury from the weighed sample with which the analysis began. Three-quarters of an hour or one hour easily covers the entire analysis from beginning to end.

For ammoniated mercury, mercury iodide red, mercury iodide yellow, and mercurous chloride, a different procedure is advisable. These salts are all dissolved in solution of sodium sulphide and from this the mercury is deposited. The samples, about 0.3 to 0.5 gram, are weighed directly into the tared mercury cathode dish. Ten mils of solution of sodium sulphide (sp. gr. 1.18) are added and a current of 0.5 to 0.75 ampere and 4 to 5 volts is passed for half an hour. Use the rotating anode running about 500 revolutions per minute. The mercury from the samples is deposited on that of the mercury cathode and all is washed and dried in the usual way with water, alcohol, and ether. If any amalgam of sodium and mercury forms during the electrolysis allow the wash water to stand on it until it is all decomposed.

Mercuric chloride is best treated in a simpler manner. To determine the mercury quickly in this place a sample of about 0.3 gram in a weighed mercury cathode dish, dissolve in 20 mils of water, and, after adding a layer of about 10 mils of toluene to protect the apparatus from chlorine gas, pass a current of about 1 ampere and 10 to 11 volts for fifteen minutes. The speed of the rotating anode to be used in this case is about 500 revolutions per minute. At the end of fifteen minutes the liquids may as usual

[1] J. Ind. & Eng. Chem. 1910, 2, 481.

be removed by decantation and the mercury cathode washed, dried and weighed.

Electrolytic Determination of Mercury in Mercury Oleates, Murray.[1]—About .7 to .1 gram of the oleate is weighed directly into a mercury cathode cup (such as a small beaker capacity 50 to 75 mils). To this sample there are added 15 to 20 mils of 10 per cent hydrochloric acid and 15 mils of toluene. The cathode cup with its contents is placed within a somewhat larger crystallizing dish or beaker which later can be filled with cold water to keep the temperature of the reaction down as desired. After attaching the anode and making the connections in the customary way, electrolysis of this non-uniform mixture is begun, gradually and slowly increasing the current up to 3 amperes, using about ten minutes to do it. The current (3 to 3.5 ampers at about 8 volts) is then maintained for about thirty minutes, the anode rotating at about 800 revolutions per minute. As the electrolysis continues, the contents of the cup become heated nearly to the boiling-point of some of the constituents, thus melting the mercury oleate. It is essential that the mercury oleate should melt. If the liquid in the cathode cup becomes too hot and appears to boil over, it should be cooled down by pouring water into the crystallizing dish or other surrounding vessel, but it should not be cooled down below 60° C. When the mercury is all deposited the cathode cup is washed out by siphonation in the customary way with water, after which the metallic mercury is washed with alcohol, dried with ether, and finally weighed.

Electrolytic Determination of Mercury in Mercury Salicylates, Murray.—Put about .3 gram into the mercury cathode dish and dissolve in 10 mils of sodium sulphide solution (sp. gr. about 1.18). To this solution are added 20 mils of 10 per cent potassium hydroxide solution. The mixture is now electrolyzed using a current of 1 ampere at 7 volts until the mercury is completely deposited, usually one-half hour being required. The anode should rotate about 500 revolutions per minute. After the deposition the electrolyte is decanted. the mercury is washed with water until free from alkalinity, then with alcohol, finally with ether, and then weighed.

Assay of Mercuric Chloride (Antiseptic) Tablets.—R. M. Chapin's[2] method for the analysis of tablets containing mercuric chloride and ammonium chloride.

Weigh 5 tablets, dissolve in water, dilute to 100 mils and pass through a dry filter, discarding the first 20 mils of filtrate. From the remainder pipette 10 mils (equivalent to one-half tablet) into a glass-stoppered 250-mil Erlenmeyer flask, add 2½ grams pure powdered potassium iodide, mix to entirely dissolve, and then wash down the sides of the flask with 20 mils of normal caustic alkali. Add exactly 3 mils of 37 per cent formaldehyde

[1] J. Ind. and Eng. Chem., 8, 1916, 257. [2] Amer. J. Pharm., 1914, 86, 1.

solution, mix thoroughly, and let stand for at least ten minutes, swirling the flask occasionally. Then wash down the sides of the flask with a mixture of 5 mils of 36 per cent acetic acid with 25 mils water; mix, and without delay run in from a burette 25 mils of N/10 iodin while constantly swirling the flask. Stopper the flask tightly, shake vigorously for three minutes, then after giving the contents a final swirling motion leave at rest for two minutes. If then no undissolved mercury can be detected at the bottom, the stopper is removed, rinsed, together with the neck of the flask, with a stream from a wash-bottle, and the excess iodin titrated with N/10 sodium thiosulphate, adding starch solution only when the iodin is nearly consumed.

Standardize the iodin solution by running a blank assay on 10 mils distilled water.

Subtract the volume of thiosulphate solution used in the assay from that used in the blank. The difference multiplied by the factor .0271 for strictly N/10 sodium thiosulphate will give the average weight of mercuric chloride per tablet. For a direct check upon the value of the sodium thiosulphate solution run an assay on 10 mils of a $2\frac{1}{2}$ per cent solution of mercuric chloride of known purity.

While mercuric chloride is the most important active ingredient of tablets made according to Wilson's formula, nevertheless ammonium chloride is an essential part of the formula, added in order to render the tablets easily soluble and to inhibit the formation of insoluble, and hence inactive, compounds of mercury. An assay of such tablets ought therefore to include an estimation of ammonium chloride, especially when a simple and convenient method is available

The method for ammonium chloride adopted is an adaptation of the process of Ronchese, which is based on the reaction between formaldehyde and a neutral ammonium salt, whereby methylenamin, $(CH_2)_6N_4$, is formed, the acid originally contained in the ammonium salt being released and becoming titratable with standard caustic alkali and phenolphthalein.

Titration by standard alkali and phenolphthalein cannot of course be conducted in presence of mercuric chloride. This difficulty, however, is easily overcome by throwing the mercury into a complex ion through the addition of potassium iodide. The method is as follows: Into each of two 150-mil Erlenmeyer flasks pipette 5 mils (one-fourth tablet) of the tablet solution previously prepared for the estimation of mercuric chloride (5 tablets per 100 mils) and add to each flask 2 mils of a 20 per cent solution of potassium iodide.

Dilute one volume of 37 per cent formaldehyde solution with three volumes of water, measure 20 mils of the mixture into a small flask, add .5 mil of phenolphthalein indicator solution, neutralize with N/10 barium hydrate or caustic alkali, then flow the solution over the sides of one of

the flasks (flask *A*) containing tablet solution, and mix well. To the other flask (flask *B*) containing tablet solution add about 65 mils water.

Now add to the flask *A* 25 mils water and titrate with N/10 barium hydrate or N/10 caustic alkali free from carbon dioxide until, by using flask *B* as a standard for comparison, a color change is perceptible (titration *A*).

Add methyl red to flask *B* and titrate with either N/10 acid or alkali as needed (titration *B*).

To titration *A* add titration *B* if performed with acid, or subtract if performed with alkali. The resultant figure multiplied by the factor .0214 for strictly N/10 alkali will give the average weight of ammonium chloride per tablet.

For a direct check upon the value of the N/10 alkali run an assay upon 5 mils of a $2\frac{1}{2}$ per cent solution of pure ammonium chloride.

Solutions, reagents, and water used should be free from carbon dioxide. Ordinarily titration *B* is very small, sometimes zero, but usually calling for the addition of a few drops of N/10 acid.

As respects the end-points with the indicators it is only possible to state that up to the present time no blue or green tablets tested by the originator presented the slightest difficulty. The characteristic colors of the indicators of course do not appear in the presence of other coloring matter, but the change of tint, if standards of comparison are used, is delicate and distinct.

Method for Determination of Mercuric Iodide in Tablets, A. W. Bender.[1]—Powder a sufficient number of tablets to represent 1 to 2 grains of iodide. Place in a 180-mil Erlenmeyer flask and add 20 mils 1–1 hydrochloric acid. Add about .5 gram potassium chlorate and stopper with glass tube reflux condenser. Digest on sand-bath until iodide is all dissolved. Cool and dilute with water to about 100 mils, removing and washing condenser. Blow out chlorin with a current of air. Filter and wash insoluble matter by decantation. Add excess of ammonia, and precipitate immediately in the cold with a slow stream of hydrogen sulphide. Let stand for a few hours and filter onto a weighed Gooch, washing with water, etc., and drying as described above in determining mercury as sulphide.

$$\text{Grams of HgS} \times 30.17 = \text{grains } HgI_2. \quad Hg \times 1.955 = HgI_2$$

Mercurial Ointments

About 2 grams of the ointment are warmed with petroleum ether and treated with 15 to 25 mils N/10 iodin. The mixture is heated until the mercury and mercuric oxide are dissolved, after which it is transferred

[1] J. Ind. and Eng. Chem., 1914, 6, 753.

to a separator, the iodin solution drawn off and the petroleum ether layer washed with water. The combined aqueous and iodin solutions are then treated with excess of potassium hydroxide, and the mercury precipitated by the addition of 3 mils formaldehyde 40 per cent and warming. The balance of the determination from this point follows either of the two outlines above described.

Determination of Mercuric Iodide in Ointments.—Hallaway [1] recommends warming 2.5 grams with potassium iodide solution, and the melted ointment shaken until the red color disappears. After cooling, the liquid is filtered into a stoppered flask, and the treatment of the ointment base repeated twice. Twenty mils of potassium hydroxide are added, followed by 3 mils of formaldehyde, and the mixture warmed and whirled. After one-half hour 25 mils of 33 per cent acetic acid are added, followed by 25 mils N/10 iodin, the mixture shaken until the mercury is dissolved, and the excess of iodin titrated as in the Chapin method for tablets.

Determination of Mercury and Iodin in Antiseptic Soaps, A. Seidell.[2]—About 10 grams of the soap is weighed into an Erlenmeyer flask and treated with 150 mils of 95 per cent alcohol and 3 to 5 mils concentrated hydrochloric acid. The solution is warmed and successive small portions of water added until a perfectly clear solution is obtained on shaking. If suspended particles are present, the solution should be filtered. A slow stream of hydrogen sulphide is then passed through the liquid for about an hour, and the sulphide is collected on a carefully prepared Gooch crucible. The fatty material present in the solution appears to have a tendency to cause the precipitate to pass through the filter, but no trouble on this account need be experienced if care is taken to use the least amount of suction possible until the precipitate has been washed several times with 95 per cent alcohol. The sulphide is then washed with carbon disulphide, alcohol, and ether, dried at 100 to 105° and weighed.

The filtrate and alcoholic washings from the sulphide are concentrated to about one-third, water added to replace the evaporated alcohol, the solution cooled and filtered from the separated fatty acids into a separatory funnel; 25 to 50 mils chloroform are added, the iodin liberated by the addition of a few drops of nitrous acid, and dissolved in the chloroform by shaking. The chloroform is then drawn off and a fresh portion added and shaken, and the procedure repeated until the whole of the iodin is removed. The combined chloroformic solutions are washed with water, and the washings shaken with fresh chloroform to recover any iodin which may have been taken up by them. Finally the chloroform solution is titrated with standard sodium thiosulphate.

The nitrous acid solution is prepared by adding to a mixture of about 10 grams of starch and 10 grams of arsenous acid contained in a 700-mil

[1] Pharm. J., 86, 405. [2] J. A. Chem. Soc., 1906, 28, 73.

Erlenmeyer flask, about 150 mils nitric acid of 1.3 sp. gr. The solution is warmed gently and the reddish fumes conducted into a bottle containing 100 mils of concentrated sulphuric acid.

Determination of Mercuric Chloride in Surgical Dressings, R. Guiter.[1] About 50 grams of the compound are mixed with about 250 mils of water in a 750-mil flask and well shaken for a few minutes; 5 grams of potassium iodide in solution are added and the whole shaken for ten minutes; 50 mils of 10 per cent sodium hydroxide are then added, followed by 25 mils of 40 per cent formaldehyde; after shaking again, for ten minutes 12 mils glacial acetic acid are added and 15 mils of N/10 iodin; after shaking again for ten minutes the excess of iodin is determined by titration with N/10 sodium thiosulphate.

Mercury in Organic Compounds

The determination of mercury in organic combination can be effected by decomposing the organic matter with sulphuric and nitric acids and, after removing any residual nitric acid by evaporation, neutralizing with ammonia, precipitating the mercury as sulphide in presence of dilute hydrochloric acid. If the circumstances warrant, the decomposition of the product may be effected in a Carius tube with fuming nitric acid, the heat being raised to a temperature of 160 to 180° for six to eight hours. After evaporating the solution, the residue is treated with dilute hydrochloric acid and the mercury precipitated as sulphide.

Separation of Mercury from Other Metals.—Calomel may be separated from bismuth subcarbonate by dissolving out the latter with dilute hydrochloric acid. The calomel is then collected on a Gooch, washed, dried, and weighed. If the tablet contains excipient insoluble in dilute acid, the calomel is then brought into solution with potassium iodide, precipitated with formaldehyde in presence of sodium hydroxide, and the precipitated mercury dissolved in acid and finally determined as sulphide, or dissolved in iodin solution in presence of acetic acid and the excess of iodin titrated.

The bismuth in the filtrate is precipitated either as the trisulphide, carbonate, or chromate, as detailed under Methods for Determining Bismuth.

Calomel and zinc sulphocarbolate are separated by dissolving out the zinc salt with water.

Bismuth subnitrate is separated from mercury and chalk by solution in dilute hydrochloric acid.

When mercury occurs with arsenic and iron, a solution of the sample acidulated with dilute hydrochloric acid, is precipitated with hydrogen sulphide. The filtrate contains the iron, which is converted into the ferric state, after boiling off the excess of hydrogen sulphide, and precipi-

[1] Pharm. Zeit. 1910, 427.

tated as hydroxide. The combined sulphides of mercury and arsenic are then digested with yellow ammonium sulphide, which dissolves the arsenic sulphide, and the residual mercury sulphide collected on a Gooch and, after the customary washing, weighed.

Mercury can be separated from copper and arsenic by precipitation with phosphorous acid in presence of hydrochloric acid. The mixture is allowed to stand in the cold for twelve hours, at the end of which period the precipitated calomel is collected on a Gooch, washed with water, dried, and weighed.

When mercury occurs with gold and arsenic, a solution of the sample free from nitric acid is treated with a clear freshly prepared solution of ferrous sulphate in the presence of a little hydrochloric acid, heated gently for a few hours until the precipitated fine gold has completely settled, filtered, and washed. The gold collecting on the filter, may be ignited and weighed, the filtrate subjected to the treatment with hydrogen sulphide, and the mercury separated from the arsenic as described above.

Mercury can be separated from copper and arsenic by treating a solution of the sample with 25 to 30 mils of saturated tartaric acid, stirring for one to two minutes, adding potassium cyanide in small amounts at a time until the solution becomes clear, stirring continually. The mercury is then precipitated with hydrogen sulphide in the cold.

COPPER

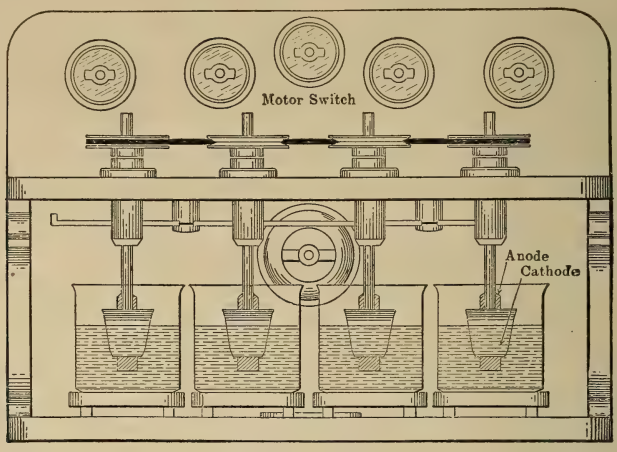
Copper salts are used in medicine because of their astringent, antiseptic properties and tonic values. They are used in remedies for diarrhea and other intestinal affections, for eye troubles, ringworm, ulcers, gonorrhea, syphilis, and in remedies for diseases of poultry, especially roup. Copper sulphate and carbonate are antidotes in phosphorus poisoning. Copper oxide, CuO, is used internally for expelling tapeworm. The acetate, arsenite, nitrate, oleate, citrate, and phosphate are all used as remedial agents. The citrate is used in ointment form for eye troubles, and is recommended for trachoma. Nucleid of copper is known as cuprol.

Copper arsenite is combined with calomel and morphin, and copper sulphate is combined with opium.

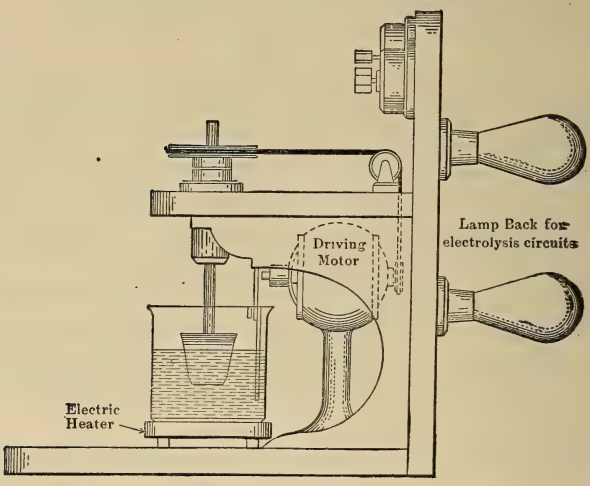
The determination of copper may be accomplished electrolytically or volumetrically. In most medicinal preparations, copper is present in the form of an inorganic salt, and in order to remove the metal from extraneous substances, the sample should be warmed with dilute hydrochloric acid, filtered, and precipitated with hydrogen sulphide. The copper sulphide is then filtered, washed with water and dissolved in hot dilute nitric acid. The determination is finished either electrolytically or volumetrically.

Electrolytic Estimation.—The solution obtained as above described is collected in a beaker of about 250-mils capacity, and two platinum elec-

trodes lowered into the liquid, the anode being a length of platinum wire, and the cathode a platinum cone or crucible. A crucible, into the mouth of which is inserted a rubber stopper which in turn is connected with a rotating spindle, will give the best results. The apparatus described below



FRONT ELEVATION



SIDE ELEVATION

will be found serviceable, and is indispensable to a well-equipped laboratory where it is necessary to perform a number of assays of copper or tin.

A current of .5 and 1 ampere passed through the copper solution will give satisfactory results. The deposition of the copper is completed when, on lowering the spindle so that a clean surface of platinum is immersed, no further coloration appears. The crucible is then detached, washed with

distilled water, and alcohol and dried at 100° for a few minutes. The gain in weight is due to the metallic copper.

Volumetric Estimation.—The hot solution is treated with sodium carbonate solution 1 per cent until a slight permanent precipitate is formed. Acetic acid is added until the precipitate is dissolved and the solution is perfectly clear. The solution is cooled and potassium iodide added in considerable excess. Each 1 gram copper requires .527 gram potassium iodide and the solution should contain at least 1 gram in excess. As soon as the precipitated cuprous iodide has settled, the iodide is titrated with standard sodium thiosulphate.

$$2(CH_3COO)_2Cu+4KI=4CH_3COOK+Cu_2I_2+I_2$$

The determination of copper in organic combination presents no serious difficulty as the organic matter can be destroyed, or at least separated from the copper, by digestion with sulphuric and nitric acid. This treatment is applicable to ointments.

GOLD

Auric chloride, $AuCl_3$, is used as a remedy for consumption, tubercular affection, and lupus. A mixture of equal parts of gold chloride and sodium chloride (gold and sodium chloride U. S. P.) is used in syphilis, cancer, hysteria, neuralgia, and rheumatism, and is the form in which the metal is usually administered for the treatment of inebriety. Aurous iodide, AuI, and aurous cyanide and auric cyanide, $Au(CN)_3+3H_2O$, are used in the treatment of scrofula and tubercular diseases. Aurous bromide and auric bromide are used as anodynes, nervines and anti-epileptics. Auric oxide, Au_2O_3, is an alterative, and is used in scrofula and tuberculosis. Potassium cyanaurate, $KAu(CN)_2$, (gold and potassium cyanide) is an active antiseptic. Collaurin is a name given to colloidal gold.

Gold salts are often present in treatments for the liquor and tobacco habits, and are combined with a variety of sedatives and narcotic drugs. In many of these remedies the quantity of gold present is exceedingly minute, and will usually be overlooked unless a special test is performed to establish its presence.

Some of the combinations listed include pill formulas where gold and sodium chloride are present with the valerianates of zinc, iron, and quinin; with arsenous acid, with arsenic chloride, and quinin· with phosphorus, Nux Vomica, and damiana.

Auric bromide is combined with bromides of arsenic and mercury in solutions.

The quantity of gold in remedial agents is often so small that its presence might easily be overlooked. In fact it may be necessary to perform

special tests to determine its presence in many instances. Solutions containing gold salts are reduced by ferrous sulphate; weak solutions yielding a bluish coloration, stronger mixtures a brown precipitate. Oxalic acid, on being gently warmed with gold salts, causes the deposition of the metal, either as a scaly precipitate or as a coherent gold film. Stannous chloride gives a precipitate or coloration (depending on the concentration) varying in color from reddish brown to purple. The presence of a trace of stannic chloride facilitates the production of the purple.

U. S. P. Assay of Gold and Sodium Chloride.—.5 gram of the substance is dissolved in 25 mils of water in a porcelain dish, 5 mils potassium hydroxide added and 5 mils hydrogen peroxide. The mixture is heated for one-half hour on a water-bath, washed with water slightly acid with hydrochloric acid, dried, ignited in a porcelain dish, and weighed. The residue should not be less than .15 gram, corresponding to at least 30 per cent of gold.

To determine the gold in pills, the ground material should be boiled with aqua regia, the solution diluted if necessary to filter off any insoluble matter, and the clear filtrate evaporated on a water-bath to the consistency of syrup, adding from time to time hydrochloric acid. The residue is dissolved in water containing hydrochloric acid, and an excess of freshly prepared clear solution of ferrous sulphate added. It is then heated gently for a few hours until the precipitated gold has completely settled, filtered, washed, ignited in a porcelain crucible or dish, and weighed.

If the sample contains iron which it is desired to determine subsequently, or if it is important to have a filtrate free from this metal, the gold may be reduced by oxalic acid. The dilute solution, freed from nitric acid as above described, is mixed in a beaker with oxalic acid or ammonium oxalate in excess, sulphuric acid added and the beaker, covered with a watch-glass, is allowed to stand for two days in a moderately warm place. The separated gold is collected in a filter, washed and ignited. If the gold solution contains a large excess of hydrochloric acid, the latter should be for the most part evaporated before the solution is diluted and oxalic acid added. If chlorides of the alkali metals are present, it is necessary that the dilution be considerable, and the time of precipitation lengthened.

BISMUTH

The well-known salts of bismuth, the subnitrate and subgallate, are valuable remedial agents for inflammatory conditions of the mucous membrane, especially of the alimentary canal; the subgallate (dermatol) is used in the local treatment of eczema, ulceration and wounds in place of iodoform; and the organic combinations are usually employed where it

is desired to combine the soothing and protective actions of the bismuth with an antiseptic. Bismuth and ammonium citrate is astringent in action, and is the form in which bismuth is usually present in elixirs. Double citrates of bismuth and lithium and of bismuth and iron are soluble scale salts.

The subnitrate and subcarbonate are dispensed in the form of pills, tablets, and powders, and the formulas often include the digestive ferments pepsin and pancreatin, with ginger and Nux Vomica. The subnitrate is also combined with calomel; with calomel and ipecac; with calomel, salol, and sodium bicarbonate; with cerium oxalate; with guaiacol carbonate; with camphor, opium, salol, and oil of peppermint; with charcoal; with opium and carbolic acid; with opium, Krameria, and licorice; with cerium oxalate and cocain.

Bismuth subgallate will be found in a few tablet formulas with Nux Vomica and digestives, and in dusting powders.

The elixir formulas containing bismuth and ammonium citrate will be found to contain in addition strychnin, the Cinchona alkaloids, ferric pyrophosphate, saccharated or lactated pepsin, and pancreatin.

Bismuth salicylate has a limited use, principally in intestinal trouble.

Milk of bismuth, or lac bismuth, is a suspension in water of a bismuth salt, usually the subcarbonate with more or less hydroxide.

Bismuth oxide is prepared in colloidal form. It is sold under trade-mark names, " Bismon " being representative of the class. It forms an opalescent colloidal suspension with water, which is not precipitated by hydrogen sulphide unless acid is present. A solution of egg albumin produces a precipitate which dissolves in excess of the albumin solution.

Tannismuth is bitannate of bismuth, containing between 17 and 21 per cent of bismuth.

Bismuth betanaphtholate, known as Orphol, is a brownish or grayish powder insoluble in water and chloroform, and slightly soluble in alcohol. It is gradually decomposed on shaking with mineral acids, and the naphthol may be recovered by shaking out with chloroform. For assaying the salt, the following procedure is used:

From 1 to 2 grams are shaken in a separator during one hour with 25 mils chloroform, and 25 mils concentrated hydrochloric acid; 50 mils of water are then added, and the mixture again shaken. The chloroform layer is then drawn off, the acid solution shaken with three portions of 10 mils of chloroform, and the combined extracts evaporated and dried over sulphuric acid, the weight amounting to at least 15 per cent. The acid solution is transferred to a beaker, diluted with water to 200 mils, heated to boiling, ammonia added until a turbidity appears, then sufficient hydrochloric acid to clear up the turbidity, and finally 50 mils of 10 per cent ammonium phosphate. When the precipitate has subsided the clear

liquid is decanted through a tared, ignited Gooch crucible, the precipitate washed by decantation with boiling water and finally transferred completely to the Gooch. It is then dried, suspended in a nickel crucible, and exposed to the full heat of the Bunsen flame until the weight is constant. The weight of the bismuth phosphate multiplied by .6869 should yield a figure representing metallic bismuth, equal to not less than 60 per cent of the material taken.

Crurin is quinolin-bismuth sulphocyanate $(C_9H_7N \cdot HSCN)_3Bi(SCN)_3$. It is a bluish-red substance, insoluble in alcohol and ether, but soluble in acetone, and slightly in glycerin. It is decomposed by water. It dissolves in dilute nitric acid, yielding a solution from which bismuth can be precipitated with hydrogen sulphide, and in which the sulphocyanide content can be determined by titration with standard silver nitrate.

Airol—Bismuth Oxyiodogallate. Airoform, $C_6H_2(OH)_3(COOBiI(OH))$

is a combination of bismuth oxyiodide (subiodide) and gallic acid. It is prepared by heating molecular quantities of bismuth subgallate and hydriodic acid or bismuth oxyiodide and gallic acid, in the presence of water, until a grayish-green product results, which is drained and dried.

It is a voluminous grayish-green, odorless, and tasteless powder, insoluble in alcohol, ether, chloroform, and olive oil, slightly soluble in glycerin. It is practically insoluble in water, communicating to water a red color on standing, slowly in the cold, but readily when heated, being decomposed with liberation of iodin and bismuth subgallate. It is readily soluble, with decomposition, in dilute alkalies and mineral acids. It is decomposed on exposure to moist air, turning red, but in admixture with glycerin and a little water it long remains unaltered.

Bismal, $4(C_{15}H_{12}O_{10})$, $3Bi(OH)_5$

is a compound of bismuth hydroxide and methylendigallic acid.

It is obtained by digesting 4 molecules of methylendigallic acid with 3 molecules of bismuth hydroxide in water.

It is a voluminous gray-brown powder, insoluble in water or gastric juice, but soluble in alkalies, forming yellowish-red solutions.

Xeroform-Tribromphenol-Bismuth

Xeroform is basic bismuth tribrom-phenolate, $Bi(C_6H_2Br_3O)_2OH \cdot Bi_2O_3$, containing nearly 50 per cent of Bi_2O_3.

According to the patent it is obtained by dissolving tribromphenol in sodium hydroxide and adding bismuth nitrate to the sodium tribromphenolate solution. The precipitated tribromphenol bismuth is collected, and washed with alcohol.

It is a fine yellow, nearly odorless and tasteless powder, neutral in reaction, and unaffected by light. It is insoluble in water, alcohol, chloroform liquid petrolatum, and vegetable oils, but soluble in 2 per cent, hydrochloric acid in the proportion of 30 : 100. By alkalies it is decomposed with the formation of bromides; it is not decomposed by heat at temperatures below 120° C., and therefore may be sterilized.

It should yield 49.5 per cent of bismuth oxide. If 1 gram is boiled with sodium hydroxide T. S. filtered, the filtrate rendered acid with sulphuric acid and the white, curdy precipitate washed and dried, it should melt at 95° C. (tribromphenol).

Bismutol is bismuth and sodium phosphosalicylate.

Helcosol is a basic compound of bismuth and pyrogallol, a yellow amorphous powder soluble slightly in very dilute hydrochloric acid, insoluble in water and alcohol.

Dermol is a combination of bismuth and chrysophanic acid, probably a basic salt. It is a yellow amorphous powder, insoluble in water and alcohol, but dissolving in nitric or sulphuric acids.

Biodal is stated to be monoiododibismuthmethylenedicresotinate. It is a pink, odorless, tasteless, insoluble powder.

Bismutose is a bismuth-albumin compound soluble in alkalies and slightly in dilute acids, but insoluble in water.

Assay of Bismuth Salts.—The bismuth content of bismuth subnitrate and subcarbonate is determined by igniting the sample in a porcelain crucible to constant weight. The Bi_2O_3 in the subnitrate amounts to not less than 79 per cent and in the subcarbonate not less than 90 per cent.

Organic salts are ignited in the same way until there is no further change in the appearance of the blackened residue. The crucible is cooled a few drops of concentrated nitric acid added, the acid evaporated over the steam-bath, and the residue carefully ignited to constant weight.

Determination of Bismuth in Mixtures.—Bismuth is determined in elixirs or in solutions of its soluble salts by evaporating the sample to dryness in a porcelain dish and igniting. The residue is then treated with concentrated nitric acid, and after the reaction due to solution of the bismuth or its oxide has ceased, the contents of the dish are warmed on the steam-bath, diluted sufficiently to prevent the acid from acting on filter paper, but not until the basic bismuth salt is thrown out; the solution filtered and washed with warm dilute nitric acid Ammonium carbonate, is added in very slight excess, heated nearly to boiling for some time, filtered onto a tared Gooch, washed with water, dried and ignited to constant weight.

When iron accompanies bismuth, the procedure should be modified. The ignited residue is dissolved in nitric acid, filtered, and evaporated until the excess of acid is drawn off. The residue is dissolved in sufficient

hydrochloric acid to hold up the oxychloride of bismuth, and subjected to the action of hydrogen sulphide until the bismuth is completely precipitated. The sulphide of bismuth is then collected on a filter and well washed with water, the filtrate and washings being preserved, if desired, for the subsequent determination of the iron. The filter paper and sulphide of bismuth are then transferred to a beaker, treated with diluted nitric acid 1–1 and heated until the bimuth is dissolved. The solution is filtered, washing through the filter with dilute nitric acid, the filtrate and washings precipitated with ammonium carbonate, and the determination completed as above described.

The bismuth content of the milk of bismuth preparations can in most instances be determined by evaporating off the water, igniting the residue, and weighing the bismuth oxide. If the composition is unusual, or impurities occur in the bismuth precipitate, it may be necessary to dissolve the basic salt in hydrochloric acid and precipitate with hydrogen sulphide, completing the determination in the usual way.

Powders containing bismuth salts in combination with digestives, antiseptics, and sodium bicarbonate should first be ignited to decompose the organic matter. The bismuth salt is then dissolved out with nitric acid and determined as usual.

In powders or tablets with calomel, bismuth salts are determined by first dissolving them in diluted hydrochloric acid in order to separate them from the calomel. The bismuth is thrown out of the filtrate as sulphide, and the determination continued.

When bismuth salts occur in complex tablet mixtures, the determination of the metal can usually be effected by burning off the organic matter by gentle ignition, treating the residue with concentrated nitric acid, and continuing to the procedure for elixirs. If zinc or other heavy metals are present, it will be necessary to evaporate the nitric acid solution to dryness, dissolve the residue in diluted hydrochloric acid, and throw out the bismuth as sulphide.

Bismuth may be determined as the trisulphide, by collecting the precipitated sulphide on a tared Gooch, washing with water, alcohol, ether, carbon bisulphide free from sulphur and finally alcohol and ether. The Gooch is then placed in a drying oven at 100° for fifteen to twenty minutes, cooled in a desiccator and weighed. There should be as little exposure as possible to the air at 100° C., as the sulphide absorbs oxygen and gains in weight $Bi_2S_3 \times .9061 = Bi_2O_3$.

Bismuth can be determined by precipitation as phosphate as described in the Assay of Orphol.

The formation of the chromate furnishes a satisfactory means of determining bismuth. The bismuth is freed from other substances by the methods described above, and a solution which is as neutral as possible

is poured, with constant stirrng, into an excess of a warm solution of potassium bichromate in a porcelain dish, washing out the vessel which contained the bismuth solution with water containing nitric acid. The precipitate should be orange yellow and dense throughout; if it is flocculent and has the color of egg yolk, there is a deficiency of bichromate and a fresh quantity of the latter must be added, and the mixture boiled until the precipitate has the proper appearance. The mixture is boiled for ten minutes and the clear supernatent liquid decanted through a tared Gooch; the precipitate is boiled with water, repeatedly decanting the washings through the Gooch, and finally collected on the filter. It is dried at 120° and weighed as $Bi_2O_3 \cdot 2CrO_3$.

Bismuth in Bismuth-β-Naphtholate-Electrolytic Determination, Murray.[1]—A sample of .3 gram is weighed into a porcelain crucible and heated very gently to decomposition of the β-naphthol. The crucible is finally heated to the full red heat of a Meker burner for three minutes to burn off the last traces of carbon. The residue resulting is yellow in color and is composed chiefly of bismuth oxide together with a small quantity of metallic bismuth. The crucible is placed in a small beaker and a mixture of 4 mils of nitric acid (sp. gr. 1.4) and 5 mils of water is added, after which it is heated on a steam-bath to complete solution. The solution is washed with distilled water into a mercury cathode cup, keeping the volume down to 20 mils. The cathode cup is conveniently made from a 50-mil Erlenmeyer flask. The 20 mils solution is then electrolyzed under the following conditions:

Current (maximum) 4.5 amperes at 6 volts.

Revolutions per minute 1000. Time forty-five minutes.

The initial application of the current is 1 ampere and this is followed by a gradual increase to 4.5 amperes. Some black masses are seen to form, but rapid rotation of the anode prevents the formation of a large quantity and all disappear, when the black masses have stopped and the cathode is washed with distilled water by siphonation while the full strength of a current is on. The electrolyte should be tested for bismuth with hydrogen sulphide. After two to three washings with water, followed by alcohol and then by ether, the mercury cathode is weighed. The increase in the weight of the mercury cathode is due to the bismuth which has been deposited on and amalgamated with the mercury.

ARSENIC

Arsenous oxide is one of the ingredients of alterative, tonic and antiperiodic remedies which are prescribed in intermittent fever, chorea, chronic rheumatism, chronic syphilitic and cancerous diseases, etc. It

[1] J. Ind. and Eng. Chem., i, 1916, 258.

is dispensed alone, and often in combination in pills and tablets with reduced iron, ferrous carbonate, strychnin, and quinin. Some of the other combinations of arsenous oxide include the following, with chinoidin, oleoresin pepper, and iron ferrocyanide (anti-chill mixture); with quinin, ferrous sulphate, Gelsemium resin, Podophyllum resin, and oleoresin pepper; with powdered black pepper, acacia, and althea; with quinin, oleoresin of Capsicum, zinc oxide, and strychnin; with extract of Eucalyptus, chinoidin, iron ferrocyanide, and Capsicum (fever and ague); with quinin, morphin, strychnin, and aconite; with quinin, Taraxacum, and ferrous sulphate; with Sumbul, asafetida, and ferrous sulphate; with quinin, strychnin, ipecac, and reduced iron; with extract Cannabis sativa and reduced iron; with ferrous carbonate, strychnin, and Hyoscyamus; with strychnin, ferrous sulphate, mercuric chloride, and potassium carbonate; with quinin, acetanilid, strychnin, Hyoscyamus, and Cannabis sativa; with ferrous sulphate, valerian, Sumbul, and asafetida; with sulphur, potassium bitartrate, sodium benzoate, ipecac, and Capsicum; with quinin, strychnin, gentian, and reduced iron; with quinin, ferric chloride, gold, and sodium chloride; with ferrous carbonate, Nux Vomica, and Cascara; with quinin, reduced iron, strychnin, and Cascara.

Arsenous oxide is sold in capsule form with cod-liver oil, creosote, atropin, and strychnin.

In the elixir form it is combined with iron pyrophosphate and quinin sulphate.

Solution of arsenous acid U. S. P. is a 10 per cent solution of arsenous oxide in dilute hydrochloric acid.

Fowler's solution or solution potassium arsenite is prepared by dissolving arsenous oxide and potassium bicarbonate in water, and adding compound tincture of lavender.

Arsenous oxide is a component of rat poisons.

Arsenic tribromide or arsenous chloride is recommended in diabetes, and is used alone and in combination with bromides of gold and mercury. Clemens' solution is prepared by adding bromin to a solution of potassium arsenite containing 1 per cent As_2O_3. The title " solution of bromide of arsenic," which is often applied to some of the preparations, is somewhat misleading, as arsenic bromide is decomposed by water into hydrobromic and arsenous acids.

Pearsons' solution is a 1/10 per cent solution (approx.) of sodium arsenate. Arsenous chloride is found in tablets combined with the chlorides of ammonium and iron and quinin hydrochlorate; and with the chlorides of iron and mercury and quinin hydrochlorate.

Arsenous iodide is used internally for the treatment of skin diseases, and externally as an ointment for the reduction of tubercular swellings. It is combined with mercuric and ferrous iodides; with the iodides of mer-

cury, iron, and potassium, mercuric chloride, and Nux Vomica. Donovan's soution is a 1 per cent aqueous solution of arsenous and mercuric iodides.

Arsenous sulphide is used internally for diseases of the skin.

Arsenic peptonate is often found in combination with the peptonate mixtures of iron and manganese.

In a discussion of the organic substances containing arsenic in combination the analyst is referred to the chapter on page 873.

Arsenous oxide is assayed according to the Pharmacopœia by treating .1 gram with 1 gram sodium bicarbonate, dissolving in 20 mils water with the aid of gentle heat, and titrating with N/10 iodin, of which not less than 20.3 mils should be required.

For the assay of the solution arsenous acid, 24.6 grams are treated with 2 grams sodium bicarbonate and 100 mils water and titrated with N/10 iodin, of which not less than 50 mils should be required.

For the assay of Fowler's solution 24.6 grams are diluted with water to 100 mils, slightly acidified, then made alkaline with sodium bicarbonate, and titrated with N/10 iodin, of which not less than 50 mils should be required.

The arsenous oxide in rat powders can be estimated by weighing out from .2 to 5. gram, mixing with 1 to 2 grams sodium bicarbonate and transferring to a 100-mil graduated flask with 25 mils water, the flask is warmed gently, but not sufficiently to gelatinize any starch which may be present. After thoroughly shaking, the contents are made up to 100 mils, and aliquots of 10 to 25 mils filtered off and titrated with N/10 iodin.

The estimation of arsenic in pills, tablets, and other mixed remedies, may be conducted as described in the chapter on General Methods.

When iron occurs with arsenic, and this is usually the case with medicinal preparations, the advisability of depending absolutely on the evolution determination may become a matter of moment, as it has been claimed that iron holds back some of the arsenic. This question is almost certain to come up in court, if the method has been used in the analysis of the preparation on which the case is based. It is probable that one will obtain all of the arsenic in the mirror from a given quantity of aliquot taken, provided he runs the determination over a sufficiently long period, and the aliquot used does not contain too much arsenic. It is advisable to run several determinations with the same solution, using different amounts, say 5, 10, 15, 20-mil portions, and note whether they check or not. As a confirmatory measure and when it is desired to determine the amount of iron present the solution containing the metals, free from organic matter, is neutralized with alkali and acidulated with hydrochloric acid. Hydrogen sulphide is passed through the mixture, which is kept warm during the treatment, until the arsenic is entirely precipi-

tated. The precipitation will be slow at first, as all of the arsenic is in the higher state of oxidation. When there is apparently no further precipitation of arsenic sulphide and sulphur and the liquid is well saturated with the gas, it is well to stopper the container and allow it to digest overnight. The sulphide and sulphur are then collected on a filter, well washed with water, and the filtrate and washing set aside for the iron determination. The filter is transferred to a beaker, covered with strong nitric acid, and heated until the sulphide has dissolved and most of the sulphur has been oxidized. The solution is somewhat diluted, a crystal or two of potassium chlorate added, and gently warmed until the odor of the gas has nearly disappeared. The solution is filtered, washed with water, the filtrate and washings treated with ammonia which must produce no precipitate or turbidity. An excess of magnesia mixture is added gradually with constant stirring and the solution allowed to stand at least twenty-four hours, after adding a further quantity of ammonia. The ammonia-magnesium arsenate is collected on a filter, washed with a mixture of ammonia and water 1 in 3. After drying the precipitate is transferred to a porcelain crucible, the filter burned and the ash added to the contents of the crucible, and the whole ignited to constant weight. $Mg_2As_2O_7$.

ANTIMONY COMPOUNDS

Antimony salts have long been used in medicine, and some of the old-time preparations which are obsolete for the treatment of human beings are employed in veterinary practice.

Antimony and potassium tartrate or Tartar Emetic is the salt most commonly employed as a medicinal agent, and is present in expectorant diaphoretic, alterative, and emetic compounds. Some of the more important formulas consist of this salt with mass of mercury, aloes and jalap (Cole's dinner pills); with ammonium chloride and Hyoscyamus; with ammonium chloride, morphin and Sanguinaria; with morphin and aconite; with morphin, aconite, and ipecac; with licorice, benzoic acid, opium, camphor, and anise oil; with ammonium chloride, senna, licorice, and sulphur; with ipecac, Sanguinaria, morphin, atropin, and aconite.

Wine of antimony is a solution of tartar emetic in wine; and compound syrup of Squill contains senega and tartar emetic.

Tartar emetic is a component of a certain type of plaster designed to produce the pustulating effect of the emetic. The base of these plasters is usually Burgundy pitch and colophony.

Sulphurated antimony or Kermes minerals is a mixture of sulphides and oxides of the metal. It is used as an alterative, diaphoretic, and emetic. Plummer Pills, a classic formula, contains Kermes mineral, calomel, and guaiac. It is also combined with ipecac and morphin; and with aconite, bryonia, belladonna, and potassium bichromate.

Antimonial saffron, Crocus Metallorum, consists chiefly of antimony oxysulphide, $Sb_2S_3+Sb_2OS_2$.

Antimony sulphide, Sb_2S_3, and antimonic sulphide, Sb_2S_5, the golden sulphide, are used in veterinary remedies.

Antimonous oxide, Sb_2O_3, is an expectorant and emetic, and is the active constituent of Antimonial powder or James' Powder (Pulvis Jacobi), a mixture with precipitated calcium phosphate.

Antimony chloride, $SbCl_3$, is used as a local application for snake bites, wounds, syphilitic ulcers, warts, and excrescences.

Antimony iodide, SbI_3, is employed in catarrh.

Antimony, when present in simple mixtures or alone as antimonous oxide, as for instance in James' powder, can be determined by titration with iodin. The powdered material amounting to about 2 grams is weighed accurately, introduced into a 250-mil graduated flask, treated with 2 grams of tartaric acid dissolved in 25 mils water, and the mixture shaken gently for sufficient time to dissolve the oxide. Sodium carbonate is added until the solution is just neutral, and the liquid made up to 250 mils. After settling, a 50-mil aliquot is drawn off into a flask and titrated with N/10 iodin. 1 mil = .0072 gram Sb_2O_3.

$$Sb_2O_3+2H_2O+2I_2=HI+Sb_2O_5$$

When antimony salts are present in pills or tablets, the sample should be well pulverized, introduced into a 250-mil graduated flask, covered with concentrated hydrochloric acid and warmed. When ebullition ceases, the solution is made up to the mark with 5 per cent tartaric acid solution and after settling, aliquots of 5 mils are drawn off, heated nearly to boiling, and hydrogen sulphide conducted through the liquid, keeping the liquid fairly hot during the passage of the gas. When thoroughly saturated, the flask is stoppered and allowed to remain in a warm place overnight. It may sometimes happen, where the quantity of antimony is small, that no precipitate will appear until the mixture has stood for some time. The sulphide is then collected on an ashless filter, washed with hydrogen sulphide water, and the filter and precipitate transferred to a tared porcelain crucible with concave lid. About eight to ten times the quantity of fuming nitric acid is added and the acid slowly evaporated on the water-bath. If charring occurs after the nitric acid has evaporated, a few more drops of the latter are added, and the evaporation repeated, and the procedure continued until no further blackening occurs. The residual mass in the crucible consists of antimonic and sulphuric acids, and on careful ignition is converted to antimony tetroxide, Sb_2O_4.

If the sulphide of antimony carries down much sulphur, the precipitate on the filter should be washed with alcohol, ether, and carbon bisul-

phide, and then with alcohol before being subjected to the acid digestion.

If mercury is simultaneously present, the sulphide precipitation may contain mercury, and in this event the filter paper containing the mixed sulphides is spread out in a porcelain evaporating dish and digested with yellow ammonium sulphide. The sulphide solution containing the antimony is filtered off, the digestion repeated and the combined filtrates and washings are treated with an excess of hydrochloric acid. The precipitated antimony sulphide is collected on a filter and the balance of the determination completed as described above.

NICKEL

The only nickel salt that has ever attained any importance in medicinal chemistry is the bromide which is employed as an antispasmodic. As it is of unusual occurrence it might be overlooked unless the label of the preparation indicated its presence. It is usually combined with codein.

A determination of the halogen is the simplest method of estimating nickel bromide. The metal may be determined by precipitating as hydroxide with potassium or sodium hydroxide. A solution of the salt is treated with an excess of the alkali and heated for some time nearly to boiling. The supernatant liquid is decanted, the hydroxide boiled up three or four times with water, decanting each time, and then brought onto the filter and thoroughly washed. After drying, the precipitate is ignited in a porcelain crucible and weighed as nickelous oxide, NiO. Instead of weighing as the oxide the latter may be reduced to the metal by ignition in a slow stream of hydrogen. The heat is applied gently at first and then more strongly until a constant weight is obtained.

With some mixtures it will be better to separate the nickel first as sulphide. A concentrated solution should be treated with ammonium chloride until nearly saturated, ammonia added until slightly alkaline, then acetic acid in slight excess. Ammonium or sodium hydroxide are then added, and the hydrogen sulphide passed through the boiling solution. If there is considerable nickel present and hence more than a small amount of acetic acid liberated, it will be necessary partially to neutralize during the process. Filter the sulphide, test the filtrate with a few drops of ammonium sulphide to determine whether the nickel has been completely thrown out, wash the precipitate with dilute hydrogen sulphide water, and dry. The precipitate is then transferred to a beaker, the filter incinerated in a porcelain crucible and the ash added to the beaker, aqua regia added, digested at a gentle heat until the sulphide is dissolved, and the undissolved sulphur appears yellow; the liquid is then diluted, filtered, and the nickel precipitated as hydroxide as described above.

If iron is present it may be removed before precipitating the nickel for its final determination, by adding ammonium chloride, and warming, adding ammonia in excess and digesting for several hours. Nickel will remain in solution. After filtering and washing, the ferric hydroxide should be dissolved in hydrochloric acid and precipitated again under the same conditions as before, adding the filtrate to that first obtained. The operation should be repeated a third time. The combined filtrates are then concentrated and the nickel determined as described.

IRON

Iron is used in medicine in the form of metallic or reduced iron; in the ferrous state (ferrous carbonate in Blaud's mass and Vallet's mass, and ferrous iodide), in the ferric state (ferric chloride); and in complex combinations. In the latter the iron does not respond to the usual reactions until the compound has been subjected to the action of a reagent capable of breaking up the complex form.

Solutions of ferric salts are used externally as styptics, and as astringents in gargles, but the principal use of iron is for the treatment of anemia, chlorosis, and conditions where a tonic or alterative is desired.

Iron salts will be encountered in several different types of pharmaceutical combinations, including pills, tablets, elixirs, wines, syrups, solutions, capsules, and gargles. The formulas are legion. The detection of iron presents no difficulties, and if present in a preparation, it will unquestionably be found during the course of the systematic analysis. The analyst may be called upon to determine the state in which the iron exists, as this feature may, in some cases, determine the efficacy of the medicine and also the claims set forth on the label. It is not enough to report that iron is present and its percentage amount given, the analyst should know whether it is in the ferrous or ferric state, and how much of each form exists as the preparation is administered.

Vallet's mass consists of ferrous carbonate which has been washed free of sodium carbonate and preserved with a saccharin mixture. Blaud's mass prepared with potassium carbonate, contains all of the potassium sulphate produced by the reaction with ferrous sulphate. Ferrous carbonate saccharated, prepared by precipitating the iron with sodium bicarbonate, consists of the ferrous salt intimately mixed with sugar.

Iron preparations often contain other metallic salts from which the metal must be separated in making a quantitative estimation, and phosphates are sometimes present, thereby complicating the analysis, and, in some cases, rendering a quantitative determination difficult or impossible.

The separation of iron from the metals of the arsenic and copper groups is of course easily effected, as these bodies are removable by hydrogen

sulphide, in presence of dilute hydrochloric acid, leaving the iron still dissolved. Iron being precipitated by ammonia in presence of ammonium chloride, can be separated from the alkali metals and the alkaline earths unless phosphates are present, in which case the alkaline earths complicate matters by precipitating simultaneously. Of its own family, the only metal of any importance accompanying iron is manganese.

With many preparations, especially syrups and elixirs, it is possible to determine iron in the same sample that has been used for determining the alkaloids. With pills and tablets the organic substances can be dissolved out with alcohol, leaving the iron salts behind for subsequent treatment dependent on the results of the qualitative investigation. Ferric chloride is of course soluble in alcohol, but this salt is seldom found except in solution, though it is combined with antipyrin as ferropyrin.

Assay of Ferrous Carbonate Saccharated.—Dissolve about 2 grams of saccharated ferrous carbonate, accurately weighed, in 15 mils of diluted sulphuric acid, and dilute the solution with distilled water to about 100 mils. Titrate immediately with N/10 potassium dichromate V. S., potassium ferricyanide T. S. being used as indicator. It shows not less than 15 per cent of $FeCO_3$.

Each mil of N/10 potassium dichromate V. S. used corresponds to .011584 gram of $FeCO_3$. Each gram of saccharated ferrous carbonate corresponds to not less than 13 mils of N/10 potassium dichromate V. S.

Reduced Iron—Assay for Metallic Iron.—Introduce about 2.6 grams of iodin into a 100-mil glass-stoppered graduated flask, weigh accurately, add 6 mils water, 2 grams potassium iodide and .555 gram reduced iron. Stopper the flask, and after thoroughly mixing the contents by rotating, set aside for one hour. Then dilute the contents with distilled water and make the liquid measure exactly 100 mils when cool, mix well, draw off 25 mils of this solution and titrate with N/10 sodium thiosulphate. Divide the weight of the iodin taken by .02518, subtract from the quotient twice the number of mils of N/10 thiosulphate used; the remainder represents the percentage of metallic iron present in reduced iron and this should not be less than 90 per cent.

The percentage purity of the iodin should be accurately determined, and in place of the 2.6 grams above directed, its equivalent of pure 100 per cent iodin may be taken.

Determination of Ferric Iron.—Ferric iron is easily determined by taking advantage of the reaction occurring in potassium iodide solution containing hydrochloric acid. The liberated iodin is titrated with N/10 sodium thiosulphate, 1 mil of which is equivalent to .00555 gram iron. A weighed amount of the salt or liquid to be tested is weighed into a glass-stoppered bottle of about 100–250 mils capacity, 2 mils of hydrochloric acid, a proper quantity of water and 1 to 2 grams potassium iodide. The

mixture is kept for one-half hour at 40° C., then cooled and the iodin titrated.

U. S. P. PRODUCTS BY THE ABOVE METHOD

Product	Sample used	Water, mils	Hydrochloric Acid, mils	Potassium Iodide, grams	Standard
Ferric chloride	1 gram dry	100	3	2	Not less than 22 mils
Ferric citrate	.555 gram	15	2	1	Not less than 16 mils
Ferric and ammonium citrate	.555 gram	15	2	1	Not less than 16 mils
Ferric and ammonium sulphate	.555 gram	15	2	1	Not less than 11.5 mils
Ferric and ammonium tartrate	.555 gram	15	2	1	Not less than 13 mils
Ferric and potassium tartrate	.555 gram	15	2	1	Not less than 15 mils
Ferric and quinin citrate (see assay following)	.555 gram		3	1	Not less than 13.5 mils
Ferric and strychnin citrate (see assay following)	1.11		4	1	Not less than 32 mils
Ferric phosphate	.555	10+40	2	1	Not less than 12 mils
Ferric phosphate (soluble)	.555	10+40	8	2	Not less than 10 mils
Solution of ferric chloride	10 mils diluted to 100 and 11.1 mils taken	10	2	1	Not less than 20 mils
Solution of ferric sub-sulphate	10 mils diluted to 100 and 11.1 mils taken	10	2	1	Not less than 27.15 mils
Solution of ferric sulphate	1.11	15	2	1	Not less than 20 mils

Colorimetric Estimation of Iron, J. S. Mayer.[1]—The originator of this method recommends it especially for assaying beef, iron, and wine, and other iron protein mixtures.

Ten mils beef, iron, and wine are diluted with distilled water to 500 mils; 5 mils of this solution are evaporated and ignited in a platinum dish, 5 mils hydrochloric acid (1–1) added, the mixture boiled an instant, poured into a 100-mil Nessler tube, water added to 100 mils, 3 drops potassium permanganate (5–1000) added to oxidize the iron, and after a few minutes 10 mils of potassium thiocyanate (20–1000) added, the color produced being immediately compared with iron standards.

Multiply the reading of the standard tube by 100 and the result will be milligrams of iron per 100 mils of sample.

The iron standards are made up according to the method of D. D.

[1] J. Amer. Pharm. Assn., 1916, 5, 517.

Jackson, by mixing definite quantities of two solutions, one containing potassium platinic chloride and the other cobaltous chloride.

ASSAY OF IRON AND QUININ CITRATE

Assay for Quinin.—Introduce 1.11 grams of the salt into a dish, and, with the aid of a gentle heat, dissolve it in 20 mils of water. Transfer the solution, together with the rinsings of the dish, to a separator, allow the liquid to become cold, then add 5 mils of ammonia water and 10 mils of chloroform, and shake the separator for one minute. Allow the liquids to separate, draw off the chloroformic layer, and shake the residuary liquid a second and a third time with portions of 10 mils each of chloroform. Allow the combined chloroformic solutions to evaporate spontaneously in a tared dish, and dry the residue at 100° C. to a constant weight. This residue should weigh not less than .1276 gram (corresponding to at least 11.5 per cent of dried quinin).

Assay for Iron.—Heat the aqueous liquid, from which the quinin has been removed in the manner just described, on a water-bath, until the odor of chloroform and of ammonia have disappeared, allow it to cool, and dilute it with water to the volume of 50 mils. Transfer 25 mils of the liquid to a glass-stoppered flask having the capacity of about 100 mils, add 3 mils of hydrochloric acid and 1 gram of potassium iodide, and after securely closing the flask, allow the mixture to stand for half an hour at 40° C. After it has been allowed to cool, it should require not less than 13.5 mils of N/10 sodium thiosulphate to discharge the color of the liquid, starch being used as indicator (each mil of the N/10 sodium thiosulphate indicating 1 per cent of metallic iron).

ASSAY OF IRON AND STRYCHNIN CITRATE

Assay for Strychnin.—Dissolve 4.44 grams of the salt in a separator, in 15 mils of water, add 5 mils of ammonia water, 10 mils of chloroform, and shake the separator for one minute. Allow the liquids to separate, draw off the chloroformic layer, and shake the residuary liquid a second and a third time with portions of 10 mils each of chloroform. Allow the combined chloroformic liquids to evaporate spontaneously in a tared dish, and dry the reside at 100° C. to a constant weight. This residue should weigh not less than .04 (.0399) gram, nor more than .0444 gram (corresponding to not less than .9 nor more than 1 per cent of strychnin).

Assay for Iron.—Heat the aqueous liquid, from which the strychnin has been removed in the manner just described, on a water-bath, until the odors of chloroform and of ammonia have disappeared, allow it to cool, and dilute it with water to the volume of 100 mils. Transfer 25 mils of the liquid to a glass-stoppered flask having the capacity of about

100 mils, add 4 mils of hydrochloric acid and 1 gram of potassium iodide, and after securely closing the flask, allow the mixture to stand for half an hour at 40° C. After it has been allowed to cool, it should require not less than 32 mils of N/10 sodium thiosulphate to discharge the color of the liquid, starch being used as indicator (each mil of N/10 sodium thiosulphate indicating one-half per cent of metallic iron).

Total iron in a pharmaceutical mixture is determined by boiling the liquid or powdered solid material with hydrochloric acid, adding a little nitric acid to oxidize any ferrous salt present, adding ammonium chloride, and excess of ammonium hydroxide and boiling until the ferric hydroxide separates. The solution is filtered and the precipitate washed with hot water, dried, ignited on the filter, and weighed as Fe_2O_3.

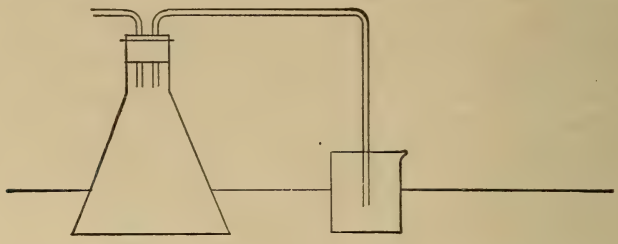
If much organic matter is present it may be necessary to pass in hydrogen sulphide after adding the ammonia and precipitate the iron as sulphide. The iron sulphide is collected on a filter, washed with water and dissolved in hot dilute hydrochloric acid. The clear liquid is boiled with the addition of a little nitric acid, ammonium chloride added and the iron precipitated with ammonium hydroxide, completing the determination as usual.

Phosphates in solution simultaneously with alkaline earth metals complicate the determination. If these substances have been indicated by the qualitative tests, the ammonium hydroxide precipitation is conducted in the usual way, the well-washed precipitated dissolved in dilute sulphuric acid, heated, and reduced with metallic zinc. Sufficient sulphuric acid is added to bring all of the zinc into solution, and the iron is then titrated immediately with permanganate.

Most of the pills and tablets which are supposed to contain ferrous salts, will contain more or less ferric iron, and an estimation of the total iron does not indicate the quantity of the ferrous salt. For quantitative purposes the solution of the organic matter with alcohol may result in the oxidation of some of the ferrous compound unless the extraction is conducted in a closed flask. The estimation of ferrous iron is accomplished in two ways.

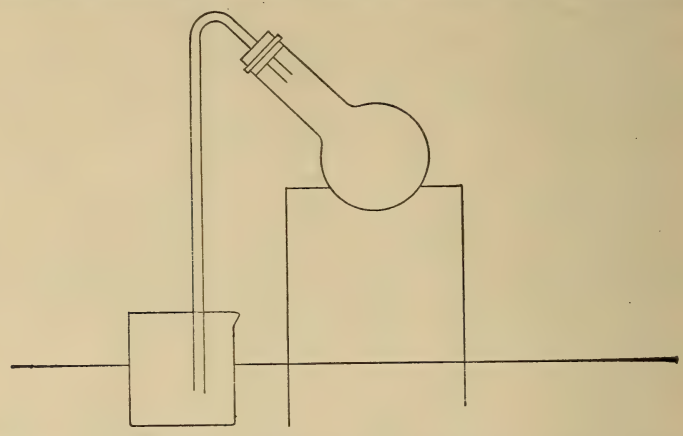
1. The finely ground substances are boiled with strong alcohol under a reflux condenser until the organic matter is dissolved. The supernatant liquid is decanted hot, the residue boiled up with a fresh portion of alcohol under the reflux, decanted again, and the procedure repeated as long as any organic matter dissolves. The flask is then fitted with a two-hole stopper containing an outlet tube which can be dipped into a beaker of recently boiled water, and an inlet tube, through which passes carbon dioxide (or the apparatus described below may be used). The substance in the flask is covered with hydrochloric acid, 1.2 sp. gr., previously boiled to expel air, a current of carbon dioxide passed into the

flask and the mixture boiled. When all traces of alcohol have been driven off and the iron salt dissolved, the outlet tube is dipped into the water, the carbon dioxide stream checked and about 25 mils of water allowed to run back into the flask. The stream of carbon dioxide is allowed to



flow slowly and the flask rapidly cooled. The stopper is withdrawn and the solution poured into a large evaporating dish which contains an acid solution of zinc sulphate prepared by dissolving 3 grams zinc in 30 mils sulphuric acid 1 in 2, 1000 mils recently boiled and cooled water added, and the whole titrated with permanganate.

If the insoluble material is dark colored and obscures the end reaction, the contents of the flask may be transferred to a graduated container of any convenient capacity, and made up to volume with recently boiled



distilled water. After the insoluble material has settled, aliquots are pipetted off and titrated.

2. About 1 gram of the finely powdered substance is weighed into a flask and boiled with a small quantity of strong hydrochloric acid diluted with about half its volume of water, until the iron salt is dissolved, using an apparatus similar to that described above or as follows:

The solution is transferred to a graduated flask of 100-mils capacity and made up to the mark with recently boiled distilled water; 25-mil

portions are then titrated with potassium bichromate. The end of the reaction is ascertained by means of a freshly prepared dilute solution of potassium ferricyanide used as an outside indicator. A number of drops of the reagent are placed upon a white plate or tile, and from time to time, during the addition of the bichromate, a drop of the solution is withdrawn on the end of a glass rod and brought in contact with one of the drops of indicator. When the reaction is complete no blue coloration is obtained. It is well to carry out a preliminary titration to determine approximately the amount of bichromate needed to complete the reaction.

The total iron in the preparation can be determined in the hydrochloric acid solution by transferring a 25-mil aliquot to a flask, heating to boiling and adding a clear freshly prepared solution of stannous chloride drop by drop, until the yellow color of the ferric chloride is just discharged. Any excess of stannous chloride is removed by adding a few drops of mercuric chloride. The iron is then titrated with bichromate.

Determination of Ferrous Hypophosphite in a Solution of the Salt.—The solution as prepared always contains a certain amount of free phosphoric acid. Weigh out the sample into a 250-mil Erlenmeyer flask, add 25 mils distilled water, 2 mils concentrated sulphuric acid, and heat to boiling. Run in N/10 permanganate gradually, until finally one drop produces a fugitive pink color. Then remove one drop of the solution on the end of a glass rod, place on a white glazed-porcelain plate and apply one drop of a very dilute solution of potassium ferricyanide. If a blue color appears, it shows that the ferrous salt has not been entirely oxidized. Continue to add permanganate gradually until on testing one drop with the ferricyanide solution there is no blue color obtained. From the number of mils of permanganate employed the amount of ferrous hypophosphite, $Fe(PH_2O_2)_2$, is calculated.

It is well to run a control experiment in the first place with a sample equal to that employed in the subsequent determination.

The iron in organic products is determined by igniting the substance and dissolving the residue in nitric and hydrochloric acid. The liquid is diluted, filtered from any carbonaceous matter, and the iron determined as usual. This procedure should be used when working with preparations of beef, iron, and wine, and whenever ammonium citrate occurs simultaneously with iron.

Iron Peptonate and Manganese Preparations.—These combinations are popular as general tonics and as remedies for chlorosis and anemia. The solutions are dark-brown in color, Ferro-Mangan, Dieterich, and Pepto-Mangan being representative. The treatment of products of this class has been described in detail under Manganese.

A distinction should be drawn between those compounds in which iron is in actual chemical combination with organic substances, and those

in which it is actually in an inorganic form, but is prevented from responding to its characteristic tests, on account of the presence of organic salts such as citrates or tartrates.

ORGANIC IRON PREPARATIONS

The term, " organic iron " is confined by modern usage to those organic compounds of iron which do not give the chemical tests of this metal until the structure of the molecule has been destroyed by reagents.

Ferratin.—Sodium Ferrialbuminate

Ferratin is the sodium salt of ferrialbuminic acid, containing iron in the ferric state in organic combination, equivalent to 6 per cent metallic iron.

Sodium ferrialbuminate occurs naturally in the organs of mammals, especially in the liver. Ferratin is prepared from egg albumin and chemically pure iron salts in the presence of alkalies.

It is a light-brown, tasteless powder, having a faint odor. It is soluble in weak alkaline aqueous solutions, from which solutions it is precipitated by hydrochloric acid. On dissolving .3 gram ferratin in 10 mils of water with the aid of a few drops of ammonia water, and then adding an equal volume of a 25 per cent potassium carbonate solution, no precipitation occurs.

Hemaboloids

Hemaboloids is a liquid said to contain in each 100 mils iron combined with proteins, equivalent to .40 gram elementary iron, proteins and nucleoproteins (nitrogen$\times$6.25) 4.0 grams, bone marrow extract 5.0 grams, nuclein .04 gram, in a menstruum containing 17 per cent alcohol by volume. It is claimed that 75 per cent of the iron is in a stable organic combination with vegetable nucleoproteins and does not react with hematoxylin, while the remaining 25 per cent is more loosely combined.

Ovoferrin

Ovoferrin is a solution containing 5 per cent of an artificial proteid-product in which iron is present in the so-called " organic " or " masked " form.

Ovoferrin is prepared by modifying serum-albumin by electrolysis, producing a proteid which is classed by the manufacturers as a vitellin, and introducing ferric hydrate into this proteid by heating under pressure. The " vitellin " constituent of this preparation should not be confounded with the well-known vitellin of yolk of eggs.

The solution has a reddish-brown color, little odor, and a flat, slightly aromatic and alcoholic taste.

The solution does not give a blue color on the addition of potassium ferrocyanide solution; a blue tint develops slowly if an equal volume of 5 per cent hydrochloric acid is added to the mixture; a deep-blue color develops at once if this mixture is boiled (difference from egg yolk).

The solution is not precipitated by boiling, but gives precipitates with the alkalies, with which it is incompatible. It is also precipitated on half saturation with ammonium sulphate. It is not precipitated by acids.

Proferrin

A compound of iron and milk casein containing iron equivalent to about 10 per cent elementary iron and phosphorus equivalent to about .5 per cent elementary phosphorus. Prepared by treating an alkaline solution of casein with a solution of an iron salt and precipitating with acetic acid. It is a brown powder, almost odorless and tasteless, insoluble in water and dilute acids, slowly soluble in alkalies. If .5 gram is shaken with 10 mils distilled water, and the mixture filtered, the filtrate should give no precipitate on addition of ammonium hydroxide, and not more than a faint bluish tint on addition of a few drops of potassium ferrocyanide solution.

If about 2 grams proferrin is digested for three hours at 40° C., with 40 mils of .2 per cent hydrochloric acid containing .006 gram pepsin, U. S. P., and the resulting mixture filtered, 5 mils of the filtrate diluted to 100 mils should produce not more than a faint-blue color on the addition of a drop of potassium ferrocyanide solution.

Triferrin

Triferrin is ferric paranucleinate; a compound of caseinparanucleinic acid with iron, containing 22 per cent of iron, 9 per cent of nitrogen and 2.5 per cent of phosphorus in neutral (organic) combination.

It is prepared by digesting cow's milk-casein with pepsin and precipitating the solution with a ferric salt.

It is a tasteless powder, soluble in weak solution of sodium hydroxide, but insoluble in weak hydrochloric acid (.1 to .3 per cent).

Hemogallol

Hemogallol is an organic iron compound produced from blood by reduction of its hemoglobin by means of pyrogallol.

Fresh defibrinated blood suitably diluted with water is mixed with an equal volume of saturated solution of pyrogallol, which causes the pre-

cipitation of a voluminous precipitate which is separated, washed with water to remove pyrogallol, and finally with alcohol.

It is a reddish-brown, almost tasteless powder, insoluble in water, alcohol, etc.

It does not show the spectroscopic absorption bands of hemoglobin between D and E.

Iron albuminate is a brown powder or scale, soluble in water. Albo-ferrin is an iron albumin compound.

Iron alginate is a brown tasteless powder obtained by precipitating a solution of sodium alginate with ferric chloride. It is soluble in ammonia.

Iron cacodylate is a grayish-yellow powder soluble in water.

Iron glycerophosphate (ferric) is a yellow powder or scale, soluble with difficulty in alcohol and water.

Ferratogen is a grayish-yellow substance obtained by growing yeast in a ferruginous medium.

Ferrostyptin is a formaldehyde-iron preparation occurring in the form of yellow crystals, soluble in water, insoluble in cold alcohol and ether.

Iron peptonate is prepared by treating an aqueous solution of beef peptone with a solution of iron oxychloride and precipitating with ammonia. In order to render the iron peptonate soluble in water, the precipitate is dissolved in ammonium citrate and the solution condensed to a thick jelly or completely dried *in vacuo*.

CHROMIUM

Chromium anhydride, so-called " Chromic Acid " CrO_3, is a caustic and astringent. It is used externally in the treatment of running sores and ulcers, to check hemmorhage, as an astringent for perspiring feet, for leucorrhea, and for foot and mouth disease.

Potassium bichromate is used in gastric ulcers and syphilis,rand externally for treating perspiring feet, tubercular elevations, warts, etc. It is combined with antimony sulphide, aconite, belladonna and Bryonia in tablets for bronchitis.

Chromium is estimated by treating a weighed amount of the chromium anhydride-containing substance, with sodium hydroxide solution, acidifying strongly with acetic acid and precipitating hot with lead acetate. The lead chromate is then filtered into a tared Gooch, washed with hot water containing a little acetic acid, then with alcohol and ether, dried and weighed.

Samples containing potassium bichromate are crushed, leached with hot water, filtered, the filtrate treated with sodium acetate and acetic acid and precipitated with lead acetate.

If drug extracts are present, and tannins and soluble gums interfere

with a lead precipitate, the whole procedure must be changed. In this case the sample is digested with dilute hydrochloric acid, the liquid filtered into a beaker, neutralized with sodium hydroxide, acidified with hydrochloric acid and subjected to the action of hydrogen sulphide until the color of the chromate has disappeared. The container is allowed to stand in a moderately warm place until the sulphur has settled, filtered into a porcelain or platinum dish and washed, the filtrate boiled to expel any residual hydrogen sulphide, cooled, ammonia added in slight excess, and the mixture exposed to a temperature approaching boiling until the liquid over the precipitate is perfectly colorless. The liquid is then decanted through a filter, the precipitate washed three times by decantation with hot water, finally brought onto the filter, washed, dried and ignited. The residue is Cr_2O_3.

ALUMINUM

Aluminum silicate is a component of antiphlogistic pastes which have attained considerable reputation. It provides the base, and is combined with glycerin, boric acid, menthol, thymol, eucalyptol, and ammonium iodide.

The double sulphate of potassium and aluminum (Alum) is a powerful astringent, used internally in painter's colic, in uterine injections and washes, and in styptic pencils. Uterine astringents and washes contain alum, zinc sulphate, morphin and Hydrastis, tannin and boric acid; and alum, boric acid, tannin, thymol, eucalyptol, salicylic acid, Helonias, Hyoscyamus, opium, and Hamamelis. Aluminum and ammonium sulphate (ammonia alum) is used for similar purposes.

Aluminum hydrate is employed in diarrhea and dyspepsia. It is sometimes combined with metallic aluminum and calcium carbonate. Aluminum acetate and chloride are used as disinfectants. Aluminum sulphocarbolate (Sozol) and aluminum naphthol-disulphonate (Alumnol) are used as substitutes for iodoform. They are both soluble in water and a solution of the latter fluoresces blue.

To determine aluminum, five to ten tablets are ground or 10 to 25 mils of a solution evaporated to dryness, and ignited, if much organic matter is present, until the mass is completely charred. The residue is extracted with warm hydrochloric acid 1–1, filtered into a beaker, made up to 150 mils, 25 mils ammonium chloride solution added and brought to a boil. Dilute ammonia is added in slight excess, the solution boiled for one minute, the precipitate allowed to settle, washed by decantation, filtering through a filter with a cotton plug. The precipitate is washed with 10 per cent ammonium nitrate solution and then burned wet, ignited to constant weight over a blast lamp and weighed as Al_2O_3.

If zinc or calcium are present they can of course be determined in the filtrate.

Phosphates and iron complicate this determination. The former are usually present in small quantity, if the tablets contain much drug extractive, and iron often occurs as an impurity. If iron is present in quantity, the ignited residue should be dissolved in aqua regia, the acid evaporated, the residue dissolved in hydrochloric acid 1 to 1, the iron reduced by adding zinc and titrated with permanganate after pouring the solution into a solution of 3 grams of zinc dissolved in 30 mils sulphuric acid 1 to 2, and 1000 mils of recently boiled distilled water.

Phosphoric acid can be estimated by dissolving the precipitate in aqua regia, evaporating, dissolving in dilute nitric acid, precipitating with ammonium molybdate and completing the determination as usual.

MANGANESE

Manganese does not functionate to a great extent in medicinal products, but it will be overlooked many times unless the analyst is watchful. It is used principally in tonic mixtures, both liquid and pill, where it accompanies iron, and it will be found in the metallic hypophosphite preparations, and in the organic tonics of the Pepto-mangan type. Manganese iodide, lactophosphate, carbonate, and citrate have a limited use, but the principal form in which manganese is dispensed is the dioxide.

The well known " pink pill " formulas consist of manganese dioxide, ferrous carbonate, gentian, strychnin, and licorice. Manganese iodide is combined with Leptandra, Juglans, Sanguinaria, and Hyoscyamus. Manganese dioxide has been reputed as an emmenagogue and should be looked for in emmenagogue pills.

Determination of Manganese.—Twenty-five mils of a liquid preparation is evaporated to dryness and gently charred, or ten to twenty pills are ground and charred. Fifteen mils of concentrated nitric acid are added to the residue, evaporated to dryness on the steam-bath, the carbonaceous matter burned at a low heat, the addition of a further quantity of acid and repetition of the evaporation being carried out if necessary. After cooling, 10 mils of concentrated hydrochloric acid are added, and the dish covered and heated on the steam-bath until the iron has gone into solution. The acid is then evaporated to dryness, a further quantity added and evaporated to a syrupy consistency. One hundred mils of cold water are added, the solution filtered into a large beaker, thoroughly washing any precipitate left on the filter. The filtrate which should amount to about 200 mils, is treated with a strong solution of sodium carbonate until the precipitate formed dissolves but slowly. The carbonate is then added carefully 2 to 3 mils at a time, with vigorous stirring, allowing several minutes to elapse between each addition to determine

whether the precipitate dissolves or not. When a decided precipitate remains, 2 drops of hydrochloric acid are added, well stirred, and the solution allowed to stand for several minutes. If it does not clear, a further 2 drops of acid are added, and this operation continued, until sufficient has been added to just dissolve the precipitate. Two grams of sodium acetate are dissolved in a little hot water and added to the solution, followed by 500 mils of boiling water, the beaker heated to boiling, and allowed to stand for ten minutes at the boiling temperature; the lamp is then removed and the precipitate allowed to settle. The supernatant liquid is decanted through a filter containing a plug of cotton, the precipitate brought onto the filter and washed with boiling water, the filtrate and washings transferred to a porcelain evaporating dish and evaporated rapidly. When the precipitate has thoroughly drained, the filter containing it is transferred to the beaker in which the precipitation was made, the iron dissolved in 10 mils concentrated hydrochloric acid and a little water, filtered into a liter beaker, washing as usual and repeating the precipitation and filtration precisely as in the first case, adding the filtrate to the first one. The evaporation is continued until about 300 mils remain and the liquid filtered into a 500-mil beaker. Ten grams of sodium acetate are added, 3 to 5 drops of acetic acid and then ammonia until the liquid is decidedly alkaline. A few mils of bromin are added, the solution stirred, heated to boiling for five minutes, occasionally adding a little bromin water. The precipitate is allowed to settle, filtered, washed with hot water, dried and ignited to constant weight over a blast lamp. The ignited substance is Mn_3O_4.

Volumetric Method for Determining Manganese.—The sample is prepared in the same way as described above, treated with 15 mils of nitric acid, sp. gr. 1.2, and boiled until nitrous fumes ceased to be given off. One gram of red lead is added, 30 mils of hot water and the mixture boiled four to five minutes. The supernatant liquid is decanted into a beaker and the residue boiled with hot water containing 20 to 25 per cent of nitric acid. The boilings and decantations are continued as long as they show a decided color, and the united decantations are filtered through asbestos which has been ignited in oxygen gas. The filtered solution is then made up to a definite volume and aliquots titrated with sodium arsenite solution.

The reagent is prepared and standardized as follows: .495 gram of sodium arsenite is dissolved in 300 mils water containing 2.5 gram sodium carbonate and diluted to 1 liter. It is run against N/100 permanganate by transferring a measured quantity of the latter to a flask, adding 50 mils water and 20 to 30 mils nitric acid 1.2 sp. gr. free from nitrous fumes, and titrating cold.

$$2Mn_2O_7 + 5As_2O_3 = 4MnO + 5As_2O_5$$

PERMANGANATES

Potassium permanganate is used as an antidote in poisoning by alkaloidal salts, as an antiseptic for wounds and running sores, as an injection in leucorrhea, etc., and to a limited extent in mouth washes. Zinc permanganate is also used as an antiseptic.

Solutions of permanganates are usually made up directly from the salt or from compressed tablets.

The percentage of actual permanganate in the salt or tablet is determined by dissolving a small quantity of the substance (.1 to .5 gram) in water, acidulating with 5 mils dilute sulphuric acid, warming to 60° C. and titrating with N/10 oxalic acid.

One mil N/10 oxalic acid = .0040842 gram $Zn(MnO_4)_2+6H_2O$.

ZINC

Zinc salts are employed as tonics and astringents. The oxide will be found in toilet and face powders combined with talc, and as an exsiccant to inflamed and excoriated surfaces. It is combined with quinin, strychnin, Capsicum, and arsenous acid in pills used for dipsomania; with antipyrin, belladonna and Castanea for whooping cough; with Hydrastin, belladonna, salicin, and pepsin for night sweats. Zinc bromide is employed in epilepsy and other spasmodic affections, combined with atropin, ergotin, lupulin, and Scutellaria. Zinc acetate will be found in astringent washes with lead acetate, berberin, and morphin. Zinc chloride is present in mouth washes and pyorrhea remedies, combined with betanaphthol, menthol, and formaldehyde. Zinc sulphate is combined with phosphorus, lupulin, and Valeriana; with alum, morphin, and Hydrastis; with lead acetate, morphin, and hydrastin; with alum, boric acid, tannin, morphin, and Hydrastis. Zinc phosphide is present in aphrodisiac pills which contain the salt by itself, and in combination with one or more of the following: Nux Vomica, reduced iron, Cannabis sativa, Hyoscyamus and Damiana. Zinc valerianate is combined with phosphorus and morphin; with phosphorus and strychnin; with the valerianates of iron, sometimes with addition of sumbul, and gold, and sodium chloride; with iron ferrocyanide, quinin, and Valeriana. Zinc sulphocarbolate is employed as an antiseptic wash and gargle, and internally as an intestinal antiseptic, where it is often combined with aloin; with bismuth salicylate; with the sulphocarbolates of calcium and sodium; and with salol, bismuth subnitrate, calomel, and pancreatin (cholera infantum tablets). Zinc permanganate is used as an astringent and antiseptic in urethritis. Zinc stearate is often used as a substitute for the oxide in dusting powders combined with acetanilid, and as an astringent in gonorrhea.

Determination of Zinc.—Zinc can usually be determined in simple mixtures by dissolving out the zinc salt with hydrochloric acid, precipitating with sodium carbonate, and igniting the zinc carbonate to constant weight. In most medicinal preparations and in talcum powders, even when iron is absent as an essential ingredient, small quantities of this element occur as an impurity, hence it is a good rule to get rid of the iron and other substances which may be thrown out by ammonia in the presence of ammonium chloride, and then precipitate the zinc as sulphide (in the presence of acetic acid if manganese is present), filter off the sulphide, dissolve it in hydrochloric acid, and precipitate as carbonate.

In the case of a powder .2 to .5 gram are used as a sample; of a tablet from 10 to 20; and of a liquid 10 to 25 mils are evaporated to dryness; if starch is present, the material is extracted with strong hydrochloric acid in the cold, but if absent it may be boiled with a moderately diluted acid, filtering into a beaker and washing thoroughly. If bismuth is present the acid solution is precipitated by hydrogen sulphide, the bismuth sulphide filtered off, the filtrate boiled to expel the excess of hydrogen sulphide, a few drops of nitric acid added to oxidize the iron, and the solution cooled, some ammonium chloride added, excess of ammonia and boiled until the iron is fully precipitated. After filtering off the iron, the warm filtrate in a flask is subjected to the action of hydrogen sulphide (if manganese is present excess of acetic acid must be added) until the zinc is completely precipitated, the flask is filled up to the neck with hydrogen sulphide water and set aside in a warm place for twelve to twenty-four hours. The zinc sulphide is collected on a filter and washed with hot water. The filter containing the zinc sulphide is transferred to a beaker, covered with an excess of hydrochloric acid 1 to 1, warmed until the hydrogen sulphide is driven off, filtered into a capacious porcelain casserole, washing with hot water. The solution is heated nearly to boiling and sodium carbonate added drop by drop until the liquid has a strong alkaline reaction, boiled a few minutes, the precipitate allowed to subside, the supernatant liquid decanted through an ashless filter, the precipitate washed three times by decantation with hot water, finally transferred to the filter, washed with hot water, and dried. The dry zinc carbonate is then tapped into a porcelain crucible and ignited to constant weight. The filter is burned in a platinum cage and the ash dropped into a crucible, treated with a few drops of nitric acid, the acid evaporated and the residue ignited at a low red heat. The product is zinc oxide, ZnO, and represents the total zinc present in the product.

When working with preparations containing zinc permanganate, the permanganate should be reduced by boiling the solution with alcohol before proceeding with the analysis. Practically all of the manganese

will separate as oxide, but the manipulation should follow the directions given above for precipitating the zinc in presence of manganese.

CERIUM

Cerium oxalate, $Ce_2(C_2O_4)_3 \cdot 9H_2O$, is employed in many forms of gastric disturbances. It is dispensed in pills and tablets either alone or in combination with bismuth subnitrate; with Nux Vomica, pepsin, creosote and cocain. The commercial salt is really a mixture of the oxalates of the so-called rare earths, the cerium predominating.

On ignition, it is converted to cerium oxide, CeO_2, which is permanent, and oxides of accompanying bases, and can be used as a means of estimation. It amounts to about 47 per cent of the weight of the oxalate. Cerium oxide, obtained by igniting the salt, when dissolved in concentrated sulphuric acid is the cause of the development of a blue color changing to purple and red on adding strychnin, and this test is of value in detecting the presence of cerium oxalate in admixtures.

Cerium oxalate can be separated from bismuth subnitrate by boiling the sample with dilute hydrochloric acid in which both dissolve, and precipitating the bismuth with hydrogen sulphide. The cerium can then be thrown out as hydroxide by adding excess of potassium hydroxide and boiling. The hydroxide is filtered off, washed with hot water, dried, and ignited.

If cerium oxalate occurs in a preparation which contains no other metallic salts, it can be determined by direct ignition of the sample and weighing the oxide.

STRONTIUM

Strontium salts have a limited use in medicine. The bromide, iodide, and salicylate are recognized in the Pharmacopœia. The peroxide is used in ointments and dusting powders.

Strontium is determined, if in the form of a soluble salt, by direct precipitation of a solution with ammonium carbonate in the presence of ammonia. If the salt is insoluble in water it is brought into solution with a minimum quantity of hydrochloric acid and precipitated as above. The container is allowed to stand for several hours in a warm place, filtered onto an ignited tared Gooch, washed with water containing a little ammonia, dried, and ignited at a low heat. Strontium carbonate, $SrCO_3$, loses its CO_2 gradually at an intense heat.

If phosphates are present they must be removed before precipitating with ammonium carbonate. If ammonia in presence of ammonium chloride produces a precipitate, and this precipitate, is found to consist in part of phosphates, sufficient hydrochloric acid is added to dissolve the pre-

cipitate, and the solution is made nearly neutral by the addition of sodium carbonate. A mixture of sodium acetate 10 per cent and acetic acid is added and the solution boiled and filtered if necessary. Ferric chloride is added to the filtrate drop by drop until precipitation is complete, at which point the liquid will begin to assume a distinct reddish color, and the mixture gently boiled for a few minutes (whereby the ferric acetate is converted into insoluble basic acetate) and then filtered. The solution now contains any zinc or manganese and the alkaline earths as chlorides and their separation and determination can follow the usual methods.

If calcium occurs simultaneously with strontium, the latter may be separated by treating the ammoniacal solution with about fifty times the quantity of the substances as weighed, of ammonium sulphate, and either boiling for some time with renewal of the water that evaporates, adding sufficient ammonia to keep the solution faintly alkaline, or allowing the determination to stand at the ordinary temperature for twelve hours. The precipitate which consists of strontium sulphate and a little ammonium strontium sulphate, is filtered, washed with a concentrated solution of ammonium sulphate, till the washings remain clear on the addition of ammonium oxalate, cautiously ignited, moistened with a little dilute sulphuric acid, reignited, and weighed. The diluted filtrate is then precipitated with ammonium oxalate for the determination of calcium.

CALCIUM

Calcium salts are used in medicinal preparations both for therapeutic and mechanical effects. Calcium carbonate and sometimes the phosphate are present in tooth powders, pastes, and face powders, and the same salts, and also calcium sulphate, will often appear in pills and tablets as diluents and coating material.

Calcium peroxide is being used to some extent in tooth powders. Calcium sulphide and iodide are extensively employed. Calcium carbonate and phosphate occur in saline and chalybeate tonic mixtures combined with the chlorides and carbonates of sodium and potassium, magnesium carbonate, reduced iron and ferrous carbonate mass. Antiacid mixtures include calcium carbonate with magnesium carbonate and sodium chloride.

Calcium hypophosphite is extensively employed in pill, tablet, and syrup form combined with the hypophosphites of sodium, potassium, manganese, iron, quinin, and strychnin, sometimes with guaiacol or creosote. Calcium hypophosphite will be found in tonic emulsions of cod-liver oil, and with petrolatum.

Calcium phosphate occurs in the saline and chalybeate mixtures described above and in pills and syrups with the phosphates of potassium, magnesium, iron, quinin and strychnin and phosphoric acid.

Calcium lactophosphate occurs in pills and syrups with the digestive ferments, and with the lactophosphates of iron, manganese, potassium, and sodium.

Calcium bromide is a remedy for epilepsy and hysteria, and is combined with the bromides of the alkali metals and ammonia.

Calcium glycerophosphate functionates as a nerve and general tonic, and is often found with alkali glycerophosphates and soluble casein.

In order to estimate calcium, consideration must be taken of the presence of any phosphates or heavy metals of the third group in the preparation under examination. If phosphates are present, they must be removed by dissolving the sample in dilute hydrochloric acid and proceeding as described for the separation of phosphates under the discussion of strontium. Any zinc or manganese can then be removed from the filtrate by adding ammonium chloride, rendering ammoniacal, and precipitating with hydrogen sulphide. The filtrate and washings from this treatment are boiled until free of hydrogen sulphide. The ammonium chloride already added should be in sufficient amount to hold up any magnesium (if this be present) from being precipitated by ammonia. The process takes the following course depending on the presence or absence of magnesium.

1. *If Magnesium is Absent.*—Ammonia is added until the liquid has a decided odor of the reagent and the liquid is heated to boiling. A warm strong solution of ammonium oxalate, to which a little ammonia has been added, is introduced in slight excess, the mixture boiled for a few minutes and allowed to settle. The clear liquid is then decanted through a well-matted Gooch, without disturbing the precipitate. The latter is washed three or four times by decantation with boiling water, allowing it to settle completely each time. The precipitate is then brought onto the filter and washed with warm water until the filtrate is free from ammonium oxalate. A flask is then inserted under the stem of the Gooch, the precipitate dissolved in a small quantity of warm hydrochloric acid, and the Gooch well washed with warm water. The solution is treated with a few mils of concentrated sulphuric acid, diluted to 250 mils with water, heated to 60 to 70° and the oxalic acid titrated with N/10 permanganate; 63 parts of oxalic acid are equivalent to 70 parts of calcium, or 1 mil N/10 $KMnO_4$ = .002 gram calcium.

2. *If Magnesium is Present.*—Ammonia is added in slight excess, followed by ammonium oxalate as long as a precipitate forms, then a further portion of the same reagent, about sufficient to convert the magnesium to oxalate (which remains in solution). The mixture is allowed to stand at the ordinary temperature for twelve hours, the supernatant liquid decanted as completely as possible, the precipitate washed once by decantation and the filtrate and washings set to one side, and the pre-

cipitate dissolved in hydrochloric acid, diluted with water, made ammoniacal and precipitated with ammonium oxalate, the mixture allowed to stand as before, washed by decantation onto the filter previously used, and the washings continued until free of ammonium oxalate. The precipitate is then dissolved in HCl, H_2SO_4 added and titrated as above described. The first filtrate contains most of the magnesium, the second portion, acidified with hydrochloric acid, is evaporated to small volume and then added to the first portion. The clear solution is then treated with an excess of sodium phosphate and the mixture stirred, care being taken to avoid touching the sides of the beaker with the stirring rod. The beaker is then covered, allowed to stand twelve hours without warming. The precipitate is collected on an ashless filter, any particles adhering to the beaker being scraped off with a piece of filter paper, washed with a mixture of 3 parts water and 1 part ammonia, sp. g. .96, until free from chlorides. The filter and precipitate are dried and then ignited in a platinum crucible. If the magnesium pyrophosphate is dark, the crucible is cooled, the salt moistened with nitric acid, the excess of acid evaporated and reignited.

Determination of Calcium in Presence of Phosphate and Absence of all Other Metallic Phosphates Except the Alkalies.—The sample is dissolved in dilute hydrochloric acid, ammonia added until a precipitate begins to form, the precipitate dissolved by the addition of a drop of hydrochloric acid, ammonium oxalate is added in excess and finally sodium acetate, the treatment of the precipitated oxalate and remainder of the determination following the procedure directed in 1 above.

MAGNESIUM

Magnesium salts are used as laxatives, refrigerants, antiacids, and diuretics. Magnesium oxide (calcined magnesia) is used in certain forms of dyspepsia, sick headache, acid conditions of the stomach, etc.; it is combined with rhubarb in tablets, and with charcoal, ginger and pepsin in lozenges. It often accompanies cascara extracts in pills, tablets, and capsules. Magnesium acetate is combined with rhubarb. Magnesium carbonate is combined with calcium carbonate and sodium chloride; and with the chlorides, sulphates, and carbonates of sodium and potassium, carbonate and phosphate of calcium, reduced iron and ferrous carbonate in saline and chalybeate tonic compounds. Magnesium phosphate is combined with the phosphates of potassium, calcium, iron, quinin, and strychnin, and phosphoric acid in tablets and syrups.

Magnesium sulphate is combined with ferrous sulphate, quassia, and sulphuric acid. This salt is a component of many of the so-called effervescent citrate of magnesia preparations. Many of these products contain

magnesium sulphate in an effervescent base of citric and tartaric acids, and sodium bicarbonate often with the addition of sodium and potassium tartrate. Magnesium citrate, the true salt, is used in effervescent combination.

Magnesium oxide is sometimes used as an absorbant material for castor oil when it is desired to adminster the latter substance in a disguised form.

The determination of magnesium when it occurs alone or in combination with the alkali metals, is effected by bringing the substance into solution with water or dilute hydrochloric acid if necessary, adding ammonium chloride followed by ammonia, which should produce no precipitate. Sodium phosphate is then added drop by drop with constant stirring until a considerable excess is present, a further quantity of ammonia added, the beaker covered and set aside for several hours. The liquid is filtered and the precipitate washed with dilute ammonia (3 to 1) until free from chloride, dried and ignited as $Mg_2P_2O_7$.

When phosphates are present or the mixture contains alkaline earth metals, the determination follows the directions given under calcium on page 1020.

Mixtures containing sugar, plant extractive, or organic matter should be incinerated before attempting to separate the magnesium. The ash is dissolved in hydrochloric acid and the estimation continued as usual. If phosphates are present in considerable quantity it will be impossible to obtain a white ash, and extreme temperatures should be avoided. As soon as the char is obtained, the dish is cooled, the mass extracted with dilute hydrochloric acid, and the liquid filtered off, washing free from acid with distilled water. The filter and carbonaceous matter is then reignited, if necessary with the addition of a small quantity of ammonium nitrate.

THE ALKALI METALS AND AMMONIUM

Sodium

Sodium salts will be encountered in a great variety of medicinal preparations. The bicarbonate usually accompanies calomel, and is often combined with acetanilid, caffein, and the bromides in headache powders and tablets. It is one of the ingredients of soda mint tablets, lithia tablets, and in a partly converted form, furnishes the effervescing feature of the granular effervescent salts.

Sodium bromide is an ingredient of a large number of headache mixtures sold in the form of powders, tablets, and liquids.

Sodium chloride is a component of nasal tablets and liquid prepara-

tions used as douches, where it is often combined with borax and other sodium salts.

Sodium hypophosphite is sold for its tonic value, and occurs with other metallic hypophosphites, quinin, and cod-liver oil emulsions. The glycerophosphate is used for the same purpose.

Sodium phosphate is an ingredient of inorganic laxative preparations "liver salts," and effervescent salts.

Sodium salicylate is used in antirheumatic remedies, often in combination with other alkali salicylates, and in migraine tablets with antipyretics, camphor monobromated, Hyoscyamus and Gelsemium.

Sodium sulphocarbolate is used as an intestinal antiseptic.

Sodium sulphite is an antiferment, and will occasionally be found in special combinations intended for certain forms of indigestion.

More than one sodium salt is often present in a single preparation. The other alkalies are used simultaneously in many instances, and the analyst may be at a loss to determine the proper acid radicle to which to attribute the metal. Often his only conclusion can be that the preparation contains the chlorides, sulphates, and phosphates of sodium, potassium, and lithium. If the importance of the analysis warrants, the quantities of the different radicles can be determined and the proper equilibrium determined by a study of the figures.

If sodium occurs as the only alkali metal, the quantity of the combination present is probably best figured from the determination of the acid radicle.

Sodium Bicarbonate

This salt when free from normal carbonate, gives no color with phenolphthalein, but does react alkaline to methyl red and methyl orange, and can be titrated with acid against these indicators. The determination of sodium bicarbonate in admixture with acetanilid and other substances of like nature has been fully described in the section dealing with those bodies.

POTASSIUM

Potassium salts enter into the composition of remedies intended for a great variety of ailments.

Several of the potassium salts, such as the acetate, bicarbonate, bitartrate, carbonate, and nitrate are reputed to possess diuretic properties, and one or the other usually is present in the common kidney pills and liquid mixtures for kidney diseases. Kidney pills also contain extract of buchu, juniper berries, Digitalis and Squill as therapeutic agents. Methylene blue is occasionally added, not only for its remedial value, but

for the sensational effect on the consumer, who is led to believe by the advertising matter that the peculiar color imparted to the urine is an indication that the remedy is producing the desired effect. Potassium nitrate is present in liquid remedies. Potassium bicarbonate is used in pills for the relief of cystitis, and may be combined with boric acid, atropin, and the extracts of buchu, triticum, Hydrangea, cornsilk, and Viburnum prunifolium. It is also present in liquid remedies for stomach troubles with rhubarb, Hydrastis, and digestives.

Potassium bichromate is a component of bronchitis pills and tablets, with aconite, belladonna, Bryonia, and sulphurated antimony. It is used as a remedy for gastric ulcer.

Potassium bitartrate, combined with sulphur, is a common household remedy.

Potassium bromide is used in sedative mixtures for nervous conditions. It is often combined with other bromides, with Hyoscyamus, Cannabis sativa, chloral, Grindelia, and Eriodictyon. Granular effervescent caffein and potassium bromide is a well-known preparation.

Potassium carbonate and ferrous sulphate furnish the well-known Blaud pills. Potassium carbonate is dispensed with aloes, and with rhubarb and Hydrastis. It is one of the ingredients of saline and chalybeate tonics, with carbonates of sodium, calcium, and magnesium, potassium sulphate, sodium and potassium chloride, calcium phosphate, reduced iron, and Vallet's mass.

Potassium chlorate is a household remedy for sore throat and is found by itself and combined with ammonium chloride, borax, and cocain.

Potassium hypophosphite is combined with other hypophosphites in tonics and remedies for nervous troubles both liquid and solid.

Potassium iodide is employed as a remedy for asthma, syphilis, scrofula, dropsy, and rheumatism. Asthma mixtures will contain potassium iodide, bromides, arsenites, Lobelia, Euphorbia pilulifera, belladonna, opium. In syphilitic preparations mercuric chloride, arsenic, and ferrous iodides, opium and Nux Vomica may accompany potassium iodide. Rheumatic formulas will include colchicin, digitalin, guaiac, Phytolacca, salicylic acid, Gelsemium, and Cimicifuga. The well-known "Sarsaparilla" and blood remedy type of preparations may contain potassium iodide, sarsaparilla, Phytolacca, Stillingia, triticum, Trifolium, Arctium lappa, Berberis aquifolium, Xanthoxylum, Bicucculla canadensis and Cascara amagra.

Potassium nitrate is combined with extract of white pine bark, wild cherry, squill, senega, ipecac, Sanguinaria, opium and methyl salicylate in white-pine compound tablets. It is combined with Aconite, opium, and camphor in cold tablets.

Potassium osmate is used to relieve night sweats of phthisis.

Potassium phosphate is used as an alterative and is combined with other phosphates in tablets and elixirs.

Potassium and sodium tartrate (Rochelle salt) is the laxative ingredient of Seidlitz mixture. It is often combined with magnesium sulphate in granular effervescent salts, and in aperient pills and elixirs it functionates with senna, cascara, colocynth, aloes, Leptandra, and juglans.

Potassium sulphate will be found in nasal tablets, saline and chalybeate tonics, and in purgative mixtures.

LITHIUM

Lithium salts are used as diuretics and antirheumatics. The benzoate is combined with potassium bicarbonate and the chloride, phosphate, and bicarbonate of sodium; also with the salicylate and Hydrangea (Lithiated Hydrangea).

Lithium carbonate and benzoate are the lithium salts present in "Lithia tablets," the other ingredients being citric acid, potassium bicarbonate, and boric acid.

Lithium carbonate is sometimes combined with sodium arsenate, and with nickel bromide, codein sulphate, ipecac, and oil of anise.

Lithium citrate is usually produced by the action of citric acid on lithium carbonate, and the salt as an individual is seldom dispensed. Granular effervescent preparations of lithium citrate contain lithium carbonate in an effervescent base of citric or tartaric acid, sodium or potassium bicarbonate, sodium phosphate, magnesium sulphate and caffein, strontium and ammonium salicylates are often included.

Lithium salicylate is combined with other alkali salicylates, manaca, colchicin, Phytolacca, and Cimicifuga.

Lithium bromide occurs with other bromides in some of the proprietary remedies for epilepsy and nervous affections.

AMMONIUM

Ammonia water is used as an ingredient of liniments, and the free gas is readily detected by holding a piece of moistened red litmus over the mouth of the bottle. Ammonia and ammonium carbonate are the essential ingredients of smelling salts.

The compound of ammonium which is most extensively used in medicine is the chloride. In cough lozenges it is dispensed alone and in combination with potassium chlorate; with cubeb, licorice, and codein; in bronchial mixtures with licorice, Tolu, cubeb, Hyoscyamus, senega, and ipecac; with licorice, opium, benzoic acid, camphor, tartar emetic, and oil of anise (brown mixture); with cocain, cubeb, and licorice; with quinin, camphor, opium, belladonna, and aconite (Coryza); with tartar

emetic, Sanguinaria, and morphin. Many liquid combinations recommended for coughs and bronchial troubles contain ammonium chloride, licorice, aromatic balsams, opium alkaloids, senega, and ipecac.

Ammonium bromide has a limited use, and may be expected in the same class of combinations which contain the bromides of the alkali metals.

Ammonium carbonate is employed as a cardiac stimulant in fevers, pneumonia, and bronchitis. It is combined with asafetida and opium; with squill, senega, and opium; and with ammonium bromide, squill, aconite, senega, grindelia, and guaiac.

Ammonium salicylate will be found in rheumatism and headache mixtures, and ammonium valerianate is used in nervous and spasmodic disorders.

ESTIMATION OF THE ALKALI METALS

General Observations.—If the sample under consideration consists of a single alkali salt of an inorganic acid, the acid radicle may be determined, and the quantity of the metal calculated therefrom.

When the determination of the metals themselves is essential the following points should be observed:

If the specimen consists of a nitrate or salt of an organic acid, it should be converted to sulphate by adding free sulphuric acid 1 to 1, evaporating and igniting.

If the sample consists of a complex mixture of drug extractive, with salts of the alkali metals, and perhaps other metallic salts, the organic matter should be destroyed completely by one of the following methods: careful ignition; boiling with aqua regia; digestion with concentrated sulphuric acid in a Kjeldahl combustion flask; combustion with sulphuric and nitric acids. If the sample is to be charred, do not carry the combustion to a complete carbon-free ash. Heat until it is well carbonized, then cool, extract with hot dilute acid, filter, wash, reignite the filter and residual carbon, extract with acid, and repeat if necessary.

If the sample contains no organic matter, nitrates, salts of organic acids, direct solution in water or dilute hydrochloric acid will usually suffice to get the desired elements in shape for subsequent manipulation.

From this point, however the solution was effected, the analysis proceeds in a systematic way, removing any heavy metals by the use of hydrogen sulphide, filtering and eliminating the alkaline earth metals by appropriate means. The solution is made up to some definite volume 100–250 c.c. and aliquots taken for the assay.

In presence of phosphates (unless the only salt present is an alkali phosphate) acidulate with hydrochloric acid, add an excess of ferric

chloride followed by sufficient ammonia to neutralize the greater portion of the free acid, mix with ammonium acetate in not too large excess and boil. Filter from the precipitated ferric phosphate at boiling temperature and wash with boiling water containing ammonium acetate. The filtrate will then contain the alkali metal free from phosphate.

Boric acid may be removed by mixing in a platinum dish the dry salt or a dry residue obtained by evaporating a liquid product with sufficient hydrofluoric acid (which leaves no residue on evaporation in a platinum dish), digesting, then adding concentrated sulphuric acid drop by drop, heating gently at first and then more strongly until the excess of sulphuric acid is completely expelled. The boric acid is expelled as fluoride of boron, BF_3, and the residue contains the metals in the form of sulphates.

Removal of Alkaline Earth Metals.—The solution rendered slightly acid with hydrochloric acid, is brought to boiling, a slight excess of ammonium hydroxide added, followed by ammonium carbonate and ammonium oxalate. After cooling the solution is filtered and the precipitate washed.

Ammonium chloride, if present, tends to hold magnesium in solution. If magnesium is present and it has been necessary to remove heavy metals, and ammonium chloride has been formed or added, the solution should first be evaporated to dryness, and the residue ignited below a red heat until ammonium salts have been driven off. After cooling it is dissolved in water and the analysis continued according to the regular program.

ESTIMATION OF POTASSIUM, SODIUM AND LITHIUM

The solution of one or more of the alkali metals, freed from other metals as above described, is rendered slightly acid with hydrochloric acid and concentrated in a porcelain or platinum dish (in the case of bromides or iodides the use of platinum must be avoided). Sufficient sulphuric acid (1 to 1) to convert all of the metal to normal sulphate is added, the evaporation continued until no further diminution in volume occurs. The residue is then ignited, using great caution in the early stages of the process to prevent loss by decrepitation. The final product is the normal sulphate of the metal, and is to be weighed as such, and the metal calculated therefrom.

It will sometimes happen that in analyzing samples which contain organic matter of certain kinds, a small amount of carbonaceous matter will persist throughout the entire assay, and yield a grayish or brownish residue after ignition. In such cases, the cooled residue should be treated with a small quantity of ammonium nitrate, and again carefully ignited.

Separation of Potassium.—The ignited sulphates of the metals obtained as above are dissolved in hot water, using at least 20 mils for each decigram of potassium oxide present, a few drops of hydrochloric acid added, and

platinum solution in excess (2.1 grams H_2PtCl_6 to 10 mils). The solution is evaporated on a water-bath to a thick paste, treated with 80 per cent alcohol, filtered onto a tared Gooch, washed thoroughly with 80 per cent alcohol both by decantation and on the filter, continuing the washing after the filtrate is colorless. Wash five to six times with 10 mils ammonium chloride saturated with potassium platinic chloride solution, then with a further quantity of 80 per cent alcohol, dry at 100° for thirty minutes and weigh.

Separation of Lithium.—The ignited sulphates obtained as above described are dissolved in water, slightly acidified with hydrochloric acid, brought to boiling, and barium chloride added gradually, with constant stirring, until in excess. The sulphate is allowed to settle out, the solution filtered off, the precipitate washed, the barium removed by ammonium sulphate, the filtrate evaporated, dried at 120°, and ignited below redness to remove ammonium salts. The residue is treated with a mixture of equal volumes absolute alcohol and anhydrous ether, digesting for at least twenty-four hours with occasional shaking and thoroughly disintegrating the salts. The liquid is decanted through a covered filter and the resdue treated with several portions of the alcohol-ether mixture. The filtrate contains the lithium salt, and the metal is estimated by evaporating the solvent and converting to sulphate.

DETERMINATION OF LITHIUM AS PHOSPHATE

The sulphate residue is dissolved in water, treated with an excess of sodium phosphate, rendered alkaline with sodium hydroxide, and evaporated to dryness. The residue is treated with enough water to dissolve the soluble salts with the aid of gentle heat, an equal volume of ammonia water added, the mixture digested for twelve hours at a gentle heat, filtered onto a tared Gooch, and the precipitate washed with an equal volume of water and ammonia water. The filtrate and washings are evaporated to dryness, the residue treated as before, and if more lithium phosphate is obtained it is added to that on the filter, washing as before. The precipitate is finally washed with alcohol and dried at 100° to constant weight. The precipitated normal lithium phosphate has the formula $2Li_3PO_4+H_2O$, and the water is completely expelled at 100°.

DETERMINATION OF POTASSIUM BY PERCHLORIC ACID

This method appeared in the Chemist Analyst, Dec. 1, 1918.

The solution of the alkali metals prepared in the usual way is freed from sulphates by barium chloride, evaporated to dryness and heated until ammonium salts are driven off—below red heat so as not to volatilize the potassium chloride. The residue is dissolved in 20 mils hot water,

sufficient perchloric acid added to combine with all the bases present, evaporated without stirring, cooled, and the residue dissolved in hot water. More perchloric acid is added and the solution evaporated until the heavy white fumes of perchloric acid are given off. After cooling, the residue is treated with 25 mils strong alcohol containing .2 per cent $HClO_4$ (1 mil 60 per cent acid to 300 mils alcohol) breaking up residue with stirring rod. The liquid is decanted through a tared Gooch containing a mat which has been washed with the above wash alcohol. Wash once again with the wash alcohol, decant and transfer the precipitate to the crucible. Wash several times with the wash alcohol, dry for an hour at 120–130°, cool and weigh as $KClO_4$.

The salt may be washed off the mat with hot water and the crucible used repeatedly.

AMMONIUM

Ammonia and ammonium salts will be found in a great variety of remedies.

Solution of ammonia gas is used in the preparation of the U. S. P. spirit and aromatic spirit, and occurs in liniments.

Ammonium chloride is an important constituent of throat tablets, cough mixtures, and antiseptic tablets. The bromide, carbonate, salicylate, and valerianate have important though probably less extended uses.

Ammonium salts, notably the citrate, occur in tonic mixtures of the beef, iron, and wine, and cod-liver extract type.

Assay of Spirit of Ammonia.—Two mils of the sample are carefully weighed in a stoppered weighing bottle, diluted with 50 mils distilled water and titrated with N/2 sulphuric acid, using litmus or methyl red as an indicator.

Estimation of Free Ammonia in Liniments, etc.—The weighed sample is introduced into a boiling flask, diluted with water, and distilled into a measured volume of N/10 hydrochloric acid or N/2 sulphuric acid colored with methyl red. The collecting flask should be watched, and if the color changes to yellow, a further measured quantity of acid is added. The free ammonia will come over during the first fifteen minutes of the distillation. The excess of acid is titrated with standard alkali.

The distilling flask of the Kjeldahl apparatus furnishes the most satisfactory receptacle for conducting this determination.

Ammonium Salts alone or in Admixture with Other Inorganic Compounds or with Non-nitrogenous Organic Substances.—The weighed sample is introduced into a boiling flask, diluted with water, treated with an excess

of concentrated sodium hydroxide and distilled into standard acid as directed above.

Ammonium Salts in Presence of Nitrogenous Organic Substances.— This determination is applicable to preparations of beef, iron, and wine and cod-liver extracts.

The weighed sample is introduced into a boiling flask, diluted with water, magnesium oxide added, and distilled into standard acid.

Estimation of Ammonium Chloride in Antiseptic Tablets (Chapin).— Into each of two 150-mil Erlenmeyer flasks pipette 5 mils of the tablet solution previously prepared for the estimation of mercuric chloride (5 tablets per 100 mils) and add to each flask 2 mils of a 20 per cent solution of potassium iodide.

Dilute one volume of 37 per cent formaldehyde solution with 3 volumes of water, measure 20 mils of the mixture into a small flask, add .5 mil of phenolphthalein indicator solution, neutralize with N/10 barium or caustic alkali, then flow the solution over the sides of one of the flasks, *A*, containing tablet solution and mix well. To the other flask, *B*, containing tablet solution add about 65 mils water.

Now add to flask *A* 25 mils water and titrate with N/10 barium or caustic alkali free from carbon dioxide until, by using flask *B* as a standard for comparison, a color change is perceptible (titration *A*).

Add methyl red to flask *B* and titrate with either N/10 acid or alkali as needed (titration *B*).

To titration *A* add titration *B* if performed with acid, or subtracted if performed with alkali. The resulting figure multiplied by the factor .0214 for strictly N/10 alkali will give the average weight of ammonium chloride per tablet.

TABLES

ATOMIC WEIGHTS

ADOPTED BY THE INTERNATIONAL COMMITTEE ON ATOMIC WEIGHTS (1915) OXYGEN = 16

Name	Symbol	Atomic Weight	Name	Symbol	Atomic Weight
Aluminum	Al	27.1	Mercury	Hg	200.6
Antimony	Sb	120.2	Molybdenum	Mo	96.0
Argon	A	39.88	Neodymium	Nd	144.3
Arsenic	As	74.96	Neon	Ne	20.2
Barium	Ba	137.37	Nickel	Ni	58.68
Bismuth	Bi	208.0	Niton (radium emanation)	Nt	222.4
Boron	B	11.0	Nitrogen	N	14.01
Bromin	Br	79.92	Osmium	Os	190.9
Cadmium	Cd	112.40	Oxygen	O	16.00
Caesium	Cs	132.81	Palladium	Pd	106.7
Calcium	Ca	40.07	Phosphorus	P	31.04
Carbon	C	12.00	Platinum	Pt	195.2
Cerium	Ce	140.25	Potassium	K	39.10
Chlorine	Cl	35.46	Praseodymium	Pr	140.6
Chromium	Cr	52.0	Radium	Ra	226.4
Cobalt	Co	58.97	Rhodium	Rh	102.9
Columbium	Cb	93.5	Rubidium	Ru	101.7
Copper	Cu	63.57	Samarium	Sa	150.4
Dysprosium	Dy	162.5	Scandium	Sc	44.1
Erbium	Er	167.7	Selenium	Se	79.2
Europium	Eu	152.0	Silicon	Si	28.3
Fluorine	F	19.0	Silver	Ag	107.88
Gadolinium	Gd	157.3	Sodium	Na	23.00
Gallium	Ga	69.9	Strontium	Sr	87.63
Germanium	Ge	72.5	Sulphur	S	32.07
Glucinum	Gl	9.1	Tantalum	Ta	181.5
Gold	Au	197.2	Tellurium	Te	127.5
Helium	He	3.99	Terbium	Tb	159.2
Holmium	Ho	163.5	Thallium	Tl	204.0
Hydrogen	H	1.008	Thorium	Th	232.4
Indium	In	114.8	Thulium	Tm	168.5
Iodin	I	126.92	Tin	Sn	119.0
Iridium	Ir	193.1	Titanium	Ti	48.1
Iron	Fe	55.84	Tungsten	W	184.0
Krypton	Kr	82.92	Uranium	U	238.5
Lanthanum	La	139.0	Vanadium	V	51.0
Lead	Pb	207.10	Xenon	Xe	130.2
Lithium	Li	6.94	Ytterbium (Neoytterbium)	Yb	172.0
Lutecium	Lu	174.0	Yttrium	Yt	89.0
Magnesium	Mg	24.32	Zinc	Zn	65.37
Manganese	Mn	54.93	Zirconium	Zr	90.6

STANDARD SOLUTIONS

Standard Sulphuric Acid, Standard Hydrochloric Acid, Standard Oxalic Acid

Equivalents per 1 *mil of standard Acid*

(To find the equivalent of any other normality, point off the proper decimal place or divide by the proper factor)

	N Acid, gram equiv.	N/2 Acid, gram. equiv.	N/50 Acid, gram equiv.
Hydrochloric Acid, HCl	0.03647	0.018235	0.0007294
Sulphuric Acid, H_2SO_4	0.049045	0.024523	0.0009809
Oxalic Acid, $H_2C_2O4+2H_2O$	0.063025	0.031512	0.001205
Aconite. Ether soluble alkaloids	0.645		
Aconitin, $C_{34}H_{47}O_{11}N$	0.64539		0.012907
Ammonia, NH_3	0.01703	0.008515	
Ammonium Acetate, $NH_4C_2H_3O_2$	0.07707		
Ammonium Carbonate, $(NH_4)_2CO_3$	0.04804		
Ammonium Carbonate, U. S. P., $NH_4HCO_3 \cdot NH_4NH_2CO_2$	0.052373		
Atropin, $C_{17}H_{13}O_3N$	0.28919		0.0057838
Barium Hydroxide, $Ba(OH)_2+8H_2O$	0.15776		
Benzaldehyde, C_7H_6O		0.0530	
Brucin, $C_{23}H_{26}O_4N_2$	0.39423		
Calcium Carbonate, $CaCO_3$	0.050035		
Calcium Hydroxide, $Ca(OH)_2$	0.037045		
Calcium Lactate, $Ca(C_3H_5O)_3$		0.05454	
Calcium Oxide, CaO	0.028035		
Cephaelin, $C_{14}H_{19}O_2N$	0.23316		
Chelerythrin, $C_{21}H_{17}O_4N$			0.006943
Cinchona. Combined alkaloids			0.0061841
Cinchonidin, $C_{19}H_{22}ON_2$	0.29420		0.005884
Cinchonin, $C_{19}H_{22}ON_2$	0.29420		0.005884
Cinnamic Aldehyde, C_9H_8O		0.033015	
Citral, $C_{10}H_{16}O$		0.076	
Cocain, $C_{17}H_{21}O_4N$	0.30318		0.0060636
Codein, $C_{18}H_{21}O_3N$	0.29918		
Codein, $C_{18}H_{21}O_3N+H_2O$	0.31719		
Coniin, $C_8H_{17}N$	0.12715		0.002543
Emetin, $C_{15}H_{21}O_2N$	0.24718		
Gelsemium Alkaloids	0.408		
Hydrastin, $C_{21}H_{21}O_6N$	0.38318		0.0076636
Ipecac. Combined alkaloids	0.240		0.0048034
Lead, Pb	0.10355		
Lead Acetate, $Pb(C_2H_3O_2)_2$	0.16257		
Lead Acetate, $Pb(C_2H_3O_2)_2+3H_2O$	0.18960		
Lead Subacetate, $Pb_2O(C_2H_3O_2)_2$	0.13706		
Lead Oxide, PbO	0.11155		
Lead Peroxide, PbO_2	0.11955		
Lithium Carbonate, Li_2CO_3	0.03694		
Lithium Citrate, $Li_3C_6H_5O_7$	0.034977		
Lithium Citrate, $Li_3C_6H_5O_7+4H_2O$	0.04699		

STANDARD SOLUTIONS—*Continued*

	N Acid, gram equiv.	N/2 Acid, gram equiv.	N/50 Acid, gram equiv.
Lithium Salicylate, $LiC_7H_5O_3$	0.14398		
Magnesium Carbonate, $(MgCO_3)_4Mg(OH)_2+5H_2O$	0.04857		
Magnesium Hydroxide, $Mg(OH)_2$		0.0148	
Magnesium Oxide, MgO	0.02016		
Manganese Dioxide, MnO_2	0.043465		
Morphin, $C_{17}H_{19}O_3N$	0.28516		0.0057032
Morphin, $C_{17}H_{19}O_3N+H_2O$	0.30318		0.0060636
Mydriatic Alkaloids combined	0.2092		
Nitrogen, N	0.014		
Nux Vomica Alkaloids combined	0.364		
Physostigmin, $C_{15}H_{21}O_2N_3$	0.27520		0.005504
Pilocarpin, $C_{11}H_{16}O_2N_2$	0.20815		0.004163
Pomegranate Bark Alkaloids	0.147		
Potassium and Sodium Tartrate, $KNaC_4H_4O_6+4H_2O$	0.14110	0.07055	
Potassium and Sodium Tartrate, Anhydrous		0.052533	
Potassium Acetate, $KC_2H_3O_2$	0.09812	0.04906	
Potassium Bicarbonate, $KHCO_3$	0.10011	0.050055	
Potassium Bitartrate, $KHC_4H_4O_6$	0.18814	0.09407	0 0037628
Potassium Carbonate, K_2CO_3	0.06910	0.03455	
Potassium Citrate, $K_3C_6H_5O_7+H_2O$	0.10812	0.05406	
Potassium Citrate, Anhydrous		0.051057	
Potassium Hydroxide, KOH	0.05611	0.028055	
Potassium Permanganate, $KMnO_4$	0.031606		
Quinin, $C_{20}H_{24}O_2N_2$	0.32421		0.0062842
Sabadilla Alkaloids	0.5984		
Sanguinaria Alkaloids	0.35		
Sodium Acetate, $NaC_2H_3O_2+3H_2O$	0.13607	0.068035	
Sodium Acetate, Anhydrous		0.04101	
Sodium Benzoate, $NaC_7H_5O_2$		0.07202	
Sodium Bicarbonate, $NaHCO_3$	0.08401	0.042005	
Sodium Biborate, $Na_2B_4O7+10H_2O$	0.19108		
Sodium Biborate, Anhydrous	0.101		
Sodium Cacodylate, $Na(CH_3)_2AsO_2$	0.1600		
Sodium Carbonate, $Na_2CO_3+H_2O$	0.06201	0.031005	
Sodium Carbonate, Anhydrous	0.0530	0.02650	
Sodium Citrate, $Na_3C_6H_5O_7+2H_2O$		0.04901	
Sodium Citrate, Anhydrous		0.04301	
Sodium Glycerophosphate, $Na_2C_3H_7PO_6$		0.10805	
Sodium Hydroxide, NaOH	0.04001	0.020005	
Sodium Salicylate, $NaC_7H_5O_3$	0.16004	0.08002	
Sodium Tartrate, $Na_2C_4H_4O_6+2H_2O$		0.057515	
Strontium Salicylate, $Sr(C_7H_5O_3)_2+2H_2O$		0.099435	
Strontium Salicylate, Anhydrous		0.9043	
Strychnin, $C_{21}H_{22}O_2$	0.33420		0.006684
Zinc Oxide, ZnO	0.040685		
Zinc Permanganate, $Zn(MnO_4)_2+6H_2O$	0.040842		

STANDARD SOLUTIONS

Standard Potassium Hydroxide, Standard Sodium Hydroxide, Standard Alcoholic Alkali

Equivalent per **1** *mil of Standard Alkali*

	N Alkali, gram equiv.	N/2Alkali, gram equiv.	N/50 Alkali, gram equiv.
Potassium Hydroxide, KOH	0.05611	0.02806	0.0011222
Sodium Hydroxide, NaOH	0.04001	0.020005	0.0008002
Acetic Acid, $HC_2H_3O_2$	0.06003	0.03002	
Acetic Acid Anhydride, $(CH_3CO)_2O$	0.05102		
Ammonia, NH_3	0.01703		
Ammonium Chloride, NH_4Cl	0.05350		
Betaeucain Hydrochloride, $C_{15}H_{21}O_2N \cdot HCl$	0.28365		
Boric Acid, H_3BO_4	0.06202	0.03101	
Borneol, $C_{10}H_{18}O$		0.07707	
Bornyl Acetate, $C_{10}H_{17}C_2H_3O_2$		0.09808	
Chloral Hydrate, $C_2HOCl_3+H_2O$	0.1654		
Carvone, $C_{10}H_{14}O$	0.15		
Camphor, $C_{10}H_{16}O$	0.1509		
Citric Acid, $H_3C_6H_5O_7+H_2O$	0.07003	0.03502	
Formaldehyde, CH_2O	0.03002		
Hydriodic Acid, HI	0.12793	0.06397	
Hydrobromic Acid, HBr	0.08093	0.04047	
Hydrochloric Acid, HCl	0.03647	0.01824	
Hypophosphorous Acid, HPH_2O_2	0.06606	0.03303	
Lactic Acid, $HC_3H_5O_3$	0.09005	0.04503	
Menthol, $C_{10}H_{20}O$		0.07808	
Menthyl Acetate, $C_{10}H_{19}C_2H_3O$		0.09909	
Methyl Salicylate, $CH_3C_7H_5O$		0.07603	
Nitric Acid, HNO_3	0.06302	0.03151	
Oxalic Acid, $H_2C_2O_4+2H_2O$	0.063025	0.03153	
Paraformaldehyde, $(CH_2O)_3$	0.03002		
Phosphoric Acid, H_3PO_4. To form K_2HPO_4 with Phenolphthalein	0.04903	0.02452	
Potassium Bitartrate, $KHC_4H_4O_6$	0.18814	0.09407	
Santalol, $C_{15}H_{26}O$		0.111105	
Sodium Bitartrate, $NaHC_4H_4O_6+H_2O$	0.1901	0.09503	
Salicylic Acid, $C_7H_7O_3$	0.138		
Sulphuric Acid, H_2SO_4	0.049045	0.024523	0.0009809
Sulphur Trioxide, SO_3	0.040035	0.02002	
Tartaric Acid, $H_2C_4H_4O_6$	0.07503	0.03751	
Trichloracetic Acid, $HC_2O_2Cl_3$	0.16339	0.08170	

FEHLING'S SOLUTION

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram. equiv.
Copper Sulphate, $CuSO_4+5H_2O$	0.03466
Copper Tartrate, $CuC_4H_4O_6+3H_2O$	0.03688
Cane Sugar (Sucrose), $C_{12}H_{22}O_{11}$ (after inversion)	0.00475
Glucose, Anhydrous, $C_6H_{12}O_6$	0.005
Lactose, Anhydrous, $C_{12}H_{22}O_{11}$	0.00678

BARIUM HYDROXIDE

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram. equiv.
Barium Hydroxide, $Ba(OH)_2+8H_2O$	0.15776
Ammonium Benzoate, $NH_4C_7H_5O_2$	0.13908
Ammonium Salicylate, $NH_4C_7H_5O_3$	0.15508
Benzoic Acid, $C_7H_6O_2$	0.12205
Hydrochloric Acid, HCl	0.03647
Salicylic Acid, $C_7H_6O_3$	0.13805
Sulphuric Acid, H_2SO_4	0.049045

BROMIN. (KOPPESCHAAR'S SOLUTION)

Usually used as N/10

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Bromin, Br	0.07992
Carbolic Acid, C_5H_6OH	0.01568
Orcin, $C_7H_6(OH)_2$	0.02068
Resorcinol, $C_6H_4(OH)_2$	0.01834
Sodiumphenolsulphonate, $NaC_6H_5O_4S+2H_2O$	0.058035
Sodiumphenolsulphonate, Anhydrous	0.04903

IODIN

Usually employed as N/10

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Iodin, I	0.12692
Acetone, $(CH_3)_2CO$	0.009675
Antimony Trioxide, Sb_2O_3	0.072
Antimony and Potassium Tartrate, $K(SbO)C_4H_4O_6+\frac{1}{2}H_2O$	0.16617
Arsenic, As (in arsenous compounds)	0.03748
Arsenic Iodide, AsI_3	0.22786
Arsenic Trioxide, As_2O_3	0.04948
Calcium Sulphide, CaS	0.03607
Formaldehyde, HCHO	0.015
Iron, Fe	0.2792
Hexamethylenetetramine, $(CH_2)_6N_4$	0.01167
Mercurous Chloride, HgCl	0.23606
Mercurous Iodide, HgI	0.32752
Mercury, Hg (in mercurous compounds)	0.2006
Methyl Salicylate, $CH_3C_7H_5O_3$	0.02535
Potassium Sulphite, $K_2SO_3+2HO_2$	0.09715
Sodium Bisulphite, $NaHSO_3$	0.05204
Sodium Sulphite, Na_2SO_3	0.06304
Sodium Thiosulphate, $Na_2S_2O_3+5H_2O$	0.24822
Sodium Thiosulphate, Anhydrous	0.15814
Sulphur Dioxide, SO_2	0.032035

POTASSIUM DICHROMATE

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Potassium Dichromate, $K_2Cr_2O_7$	0.049033
Glycerin, $C_3H_5(OH)_3$	0.06549
Ferrous Carbonate, $FeCO_3$	0.11584
Ferrous Sulphate, $FeSO_4+7H_2O$	0.27802
Ferrous Sulphate, Anhydrous	0.15191
Iron, Fe (in Ferrous Compounds)	0.05584
Lactic Acid, $HC_3H_5O_3$	0.02254
Sodium Thiosulphate, $Na_2S_2O_3+5H_2O$	0.24822

POTASSIUM PERMANGANATE

Usually employed as N/10

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Potassium Permanganate, $KMnO_4$	0.031606
Calcium Dioxide, CaO_2	0.036
Calcium Oxide CaO, (as oxalate)	0.28035
Ferrous Carbonate, $FeCO_3$	0.11584
Ferric Oxide, Fe_2O_3	0.07985
Ferrous Oxide, FeO	0.07184
Ferrous Sulphate, $FeSO_4+7H_2O$	0.27802
Ferrous Sulphate, Anhydrous	0.15191
Glycerin, $C_3H_5(OH)_3$	0.046
Hydrogen Dioxide, H_2O_2	0.017008
Iron in ferrous compounds, Fe	0.05584
Magnesium Dioxide, MgO_2	0.02
Oxalic Acid, $H_2C_2O_4+2H_2O$	0.063025
Oxygen, O	0.008
Potassium Chlorate, $KClO_3$	0.020427
Sodium Dioxide, Na_2O_2	0.03786
Sodium Chlorate, $NaClO_3$	0.017743
Sodium Nitrite, $NaNO_2$	0.034505
Sodium Oxalate, $Na_2C_2O_4$	0.067
Strontium Dioxide, SrO_2	0.061
Zinc Dioxide, ZnO_2	0.048

POTASSIUM SULPHOCYANATE

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Potassium Sulphocyanate, KSCN	0.09718
Mercuric Iodide, HgI_2	0.22722
Mercuric Nitrate, $Hg(NO_3)_2$	0.16231
Mercuric Oxide, HgO	0.1083
Mercury, Hg	0.1003
Silver, Ag	0.10788
Silver Nitrate, $AgNO_3$	0.16989
Silver Oxide, Ag_2O	0.11588

SILVER NITRATE

Usually employed as N/10

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Silver Nitrate, $AgNO_3$	0.16989
Allyl Iso-thiocyanate, C_3H_5SCN	0.04956
Ammonium Bromide, NH_4Br	0.09796
Ammonium Chloride, NH_4Cl	0.05350
Ammonium Iodide, NH_4I	0.14496
Arsenous Iodide, AsI_3	0.15191
Bromin, Br	0.07992
Calcium Bromide, $CaBr_2+2H_2O$	0.11797
Calcium Bromide, Anhydrous	0.099955
Calcium Chloride, $CaCl_2+2H_2O$	0.073511
Calcium Chloride Anhydrous	0.0555
Calcium Hypophosphite, $Ca(PH_2O_2)_2$	0.02836
Chlorine, Cl	0.03546
Ferrous Bromide, $FeBr_2$	0.10784
Ferrous Iodide, FeI_2	0.15484
Hydriodic Acid, HI	0.12793
Hydrobromic Acid, HBr	0.08093
Hydrochloric Acid, HCl	0.03647
Hydrocyanic Acid, HCN (to first formation of precipitate)	0.05404
Hydrocyanic Acid, (with potassium chromate as indicator)	0.02702
Iodin, I	0.12692
Lithium Bromide, LiBr	0.08686
Lithium Chloride, LiCl	0.0424
Phosphoric Acid, H_3PO_4	0.032687
Potassium Bromide, KBr	0.11902
Potassium Chloride, KCl	0.07456
Potassium Cyanide, KCN (to first formation of precipitate)	0.13022
Potassium Hypophosphite, KPH_2O_2	0.03472
Potassium Iodide, KI	0.16602
Potassium Nitrate, KNO_3	0.10111
Potassium Sulphocyanate, KSCN	0.09718
Sodium Bromide, NaBr	0.10292
Sodium Chloride, NaCl	0.05846
Sodium Cyanide, NaCN (to first formation of precipitate)	0.09802
Sodium Hypophosphite, $NaPH_2O_2+H_2O$	0.035357
Sodium Iodide, NaI	0.14992
Sodium Nitrate, $NaNO_5$	0.08501
Sodium Phosphate, $Na_2HPO_4+12H_2O$	0.11941
Sodium Phosphate, Anhydrous	0.04735
Strontium Bromide, $SrBr_2+6H_2O$	0.17779
Strontium Chloride, $SrCl_2+6H_2O$	0.13332
Strontium Iodide, SrI_2+6H_2O	0.22479
Zinc Chloride, $ZnCl_2$	0.068145

SODIUM CHLORIDE

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.
Sodium Chloride $NaCl$	0.05846
Silver, Ag	0.10788
Silver Nitrate, $AgNO_3$	0.16989
Silver Oxide, Ag_2O	0.11588

SODIUM THIOSULPHATE

Usually employed as N/10 *solution*

EQUIVALENT PER 1 MIL OF STANDARD SOLUTION

	N Solution, gram equiv.	N 2 Solution, gram equiv.
Sodium Thiosulphate, $Na_2S_2O_3+5H_2O$	0.24822	0.12411
Bromin, Br.	0.07992	
Chlorine, Cl	0.03546	
Chromium Trioxide, CrO_3	0.03333	
Copper Sulphate, $CuSO_4+5H_2O$	0.24972	
Copper Sulphate, Anhydrous	0.15964	
Iodin, I.	0.12692	0.06346
Iodin, I (from thyroid glands)		0.01058
Iodin, I (thymol iodide)	0.02115	
Iron, Fe (in ferric salts)	0.05584	
Lead Peroxide, PbO_2	0.1195	
Mercuric Chloride, $HgCl_2$	0.271	
Potassium Bromate, $KBrO_3$	0.027837	
Potassium Dichromate, $L_2Cr_2O_7$	0.049033	
Sodium Arsenate, $Na_2HAsO_4+7H_2O$	0.15604	
Sodium Arsenate, Anhydrous	0.092985	
Salicylic Acid, $C_7H_6O_3$	0.06885	
Thymol, $C_{10}H_{14}O$	0.075056	

REAGENTS

Test Solution and Indicators

The solutions have been made to conform as nearly as practicable with those given in the Pharmacopœia, and in most cases directions for preparation are given on the basis of 100-mil quantities.

Whenever the word " water " is used it is understood to mean " distilled water."

Acid, Acetic Glacial.	
Acid, Acetic, 36 per cent.	35 mils glacial acid with 65 mils water.
Acid, Acetic Dilute, 10 per cent.	6 mils glacial with 94 mils water.
Acid, Hydrochloric Conc.	
Acid, Hydrochloric Dilute, 10 per cent.	30 mils hydrochloric acid conc. with 70 mils water.
Acid, Nitric Conc.	
Acid, Nitric Dilute, 10 per cent.	11 mils nitric acid conc. with 89 mils water.
Acid, Sulphuric Conc.	
Acid, Sulphuric Dilute, 10 per cent.	7 mils sulphuric acid conc. with 93 mils water.
Alcohol, 95 per cent.	
Ammonia Water (stronger) 28 per cent.	
Ammonia Water Dilute, 10 per cent.	36 mils stronger ammonia water with 64 mils water.
Ammonium Carbonate.	20 grams ammonium carbonate U. S. P. dissolved in 20 mils ammonia water 10 per cent and 80 mils water.
Ammonium Molybdate.	10 grams molybdic acid dissolved in 42 mils ammonia water 10 per cent and poured into a mixture of 63 mils water and 63 mils nitric acid conc.
Ammonium Oxalate.	4 grams dissolved in 100 mils water.
Ammonium Sulphate.	10 grams dissolved in 100 mils water.
Ammonium Sulphide.	6 mils ammonia water 10 per cent are saturated with hydrogen sulphide and then diluted with 40 mils ammonia water 10 per cent. To prepare the yellow ammonium sulphide add 1 to 2 grams of sulphur and shake until dissolved.
Ammonium Vandate. (Mandelin's Reagent.)	1 gram dissolved in 100 mils sulphuric acid conc.
Azolitmin.	1 gram dissolved in 80 mils water and 20 mils alcohol. Place in tightly stoppered bottle and expose to temperature of steam for one hour.
Barium Chloride.	10 grams dissolved in 100 mils water.
Barium Hydroxide.	Saturated solution.
Bromin Water.	3 mils dissolved in 100 mils water. Freshly prepared.
Cadmium and Potassium Iodide.	5 grams of equal parts by weight of the two salts dissolved in 100 mils water.
Cadmium Chloride.	10 grams dissolved in 100 mils water.
Calcium Chloride.	10 grams dissolved in 100 mils water.
Calcium Hydroxide.	Saturated solution.

Calcium Hypochlorite.	10 grams triturated with 20 mils water, filtered and repeated and the filtrate made up of 100 mils.
Calcium Sulphate.	Saturated solution.
Chlorine Water.	0.5 gram potassium chlorate treated with 2 mils hydrochloric acid conc. in a flask fitted with a perforated stopper, warmed on steam-bath and when the flask is full of gas add 100 mils water.
Cobalt Nitrate.	10 grams dissolved in 100 mils water.
Cobaltous Chloride.	2 grams dissolved in 100 mils water and 1 mil hydrochloric acid.
Cochineal.	1 gram macerated with 20 mils alcohol and 60 mils water for four days. Then filtered.
Congo Red.	0.5 gram dissolved in 90 mils water and 10 mils alcohol.
Copper Acetate.	1 gram dissolved in 1000 mils water. If solution becomes cloudy add few drops acetic acid until clear.
Copper Ammonium Sulphate.	To be freshly made. To a solution of copper sulphate add ammonia until precipitate first formed is not quite dissolved.
Copper Sulphate.	10 grams dissolved in 100 mils water.
Fehling's Solution.	(1) 7 grams copper sulphate dissolved in 100 mils water. (2) 35 grams Rochelle salt and 10 grams sodium hydroxide dissolved in 100 mils water.
Formaldehyde-Sulphuric Acid. (Marquis Reagent)	10 mils formaldehyde solution in 50 mils sulphuric acid.
Fuchsin-Sulphurous Acid.	0.5 gram fuchsin and 9 grams sodium bisulphite dissolved in 500 mils water and treated with 10 mils hydrochloric acid.
Gold Chloride.	3 grams dissolved in 100 mils water.
Hematoxylin.	0.2 gram dissolved in 100 mils alcohol.
Iodeosin.	0.1 gram dissolved in 100 mils alcohol.
Iodin (Wagner's Reagent).	2 grams with 6 grams potassium iodide dissolved in 100 mils water.
Iron Chloride (Ferric).	10 grams dissolved in 100 mils of recently boiled water.
Iron Sulphate (Ferrous).	To be freshly made; 1 gram dissolved in 10 mils of recently boiled water.
Lead Acetate.	10 grams dissolved in 100 mils water.
Lead Acetate. Alcoholic.	3 grams of crystals dissolved in 100 mils alcohol.
Lead Subacetate.	18 grams lead acetate dissolved in 70 mils water, added to 11 grams of lead oxide (Litharge, PbO) in a porcelain dish, boiled for one-half hour, filtered and made up to 100 mils.
Litmus.	Exhaust the powder three times with boiling alcohol, each treatment consuming an hour. Treat residue with an equal weight of cold water and filter. Then exhaust with five times its weight of boiling water, cool and filter.

Magnesia Mixture.	10 grams magnesium sulphate and 20 grams ammonium chloride dissolved in 80 mils water and 42 mils ammonia water 10 per cent added.
Magnesium Sulphate.	10 grams dissolved in 100 mils water.
Mercuric Chloride.	5 grams dissolved in 100 mils water.
Mercuric Chloride. Alcoholic.	6 grams dissolved in 100 mils alcohol 95 per cent.
Mercuric Nitrate.	40 grams red mercuric oxide dissolved in 45 grams of nitric acid (conc.) and 15 mils water.
Mercuric-Potassium Iodide. (Mayer's Reagent).	1.3 grams mercuric chloride dissolved in 60 mils water added to 5 grams potassium iodide dissolved in 10 mils water and made up to 100 mils.
Mercurous Nitrate.	10 grams in 100 mils water. Keep over metallic mercury.
Methyl Orange.	1 gram dissolved in 1000 mils water.
Methyl Red.	0.2 gram dissolved in 100 mils alcohol.
Millon's Reagent.	10 grams mercury dissolved in 10 grams nitric acid (conc.) with the aid of heat, and then diluted with two volumes of water.
Oxalic Acid.	5 grams dissolved in 100 mils water.
Palladous Chloride.	5 grams dissolved in 100 mils water.
Phenolphthalein.	1 gram dissolved in 50 mils alcohol and 50 mils water added.
Phosphomolybdic Acid. (Sonnenschein's Reagent).	Prepare ammonium phosphomolybdate and, after washing with water, boil with nitric acid and expel ammonia, evaporate to dryness and dissolve in 10 per cent nitric acid.
Phosphotungstic Acid. (Scheibler's Reagent).	20 grams sodium tungstate and 15 grams sodium phosphate dissolved in 100 mils water containing a little nitric acid.
Picric Acid (Hager's Reagent).	1 gram dissolved in 100 mils water.
Platinic Chloride.	13 grams dissolved in 100 mils water.
Potassium Bromide-Bromate.	To a concentrated solution of potassium hydroxide add bromine to saturation, boil off excess and dilute with an equal volume of water.
Potassium-cadmium Iodide. (Marme's Reagent).	2 grams cadmium iodide added to a boiling solution of 4 grams of potassium iodide in 12 mils water and mixed with an equal volume of saturated solution potassium iodide.
Potassium Carbonate.	10 grams recently dehydrated at 130° C., dissolved in 100 mils water.
Potassium Chromate.	10 grams dissolved in 100 mils water.
Potassium Cyanide.	To be freshly prepared. 1 gram dissolved in 10 mils water.
Potassium Dichromate.	10 grams dissolved in 100 mils water.
Potassium Ferricyanide.	10 grams dissolved in 100 mils water, freshly made.
Potassium Ferrocyanide.	10 grams dissolved in 100 mils water.
Potassium Hydroxide.	6 grams dissolved in 94 mils water.
Potassium Iodide.	20 grams dissolved in 100 mils water.
Potassium Permanganate.	0.5 gram dissolved in 100 mils water.

Potassium Sulphate.	1 gram dissolved in 100 mils water.
Potassium Sulphocyanide.	1 gram dissolved in 100 mils water.
Pyrogallol Alkaline.	To be freshly made as wanted; 14 mils 25 per cent pyrogallol in water and 86 mils 60 per cent potassium hydroxide.
Resorcinol.	1 gram dissolved in 100 mils water.
Rosolic Acid.	1 gram treated with 10 mils alcohol followed by 100 mils water.
Silver Nitrate.	5 grams dissolved in 100 mils water.
Silver Nitrate, Ammoniacal.	5 grams silver nitrate dissolved in 100 mils water and treated with ammonia water 10 per cent until precipitate is not quite redissolved.
Silver Sulphate.	1 gram treated with 100 mils of water. To be filtered as used.
Sodium Acetate.	10 grams dissolved in 100 mils water.
Sodium Bisulphite.	To be freshly made; 30 grams dissolved in 100 mils water. If sulphur dioxide odor is strong add 20 per cent sodium hydroxide until scarcely noticeable.
Sodium Bitartrate.	3.5 grams tartaric acid boiled with 80 mils water, sodium carbonate added until neutral and then 3.5 grams tartaric acid added and solution made up to 100 mils.
Sodium Carbonate.	10 grams dissolved in 100 mils water.
Sodium-Cobaltic Nitrite.	4 grams cobalt nitrate and 10 grams sodium nitrite dissolved in 50 mils water, 2 mils acetic acid 36 per cent added and then water to 100 mils.
Sodium Cyanide.	To be freshly prepared. 1 gram dissolved in 10 mils water.
Sodium Hydroxide.	6 grams dissolved in 94 mils water.
Sodium Hypobromite.	1 mil bromin dissolved in 15 mils water containing 4 grams sodium hydroxide, then diluted to 20 mils. To be freshly prepared.
Sodium Hypochlorite.	9 grams calcium hypochlorite triturated with 20 mils water, filtered and repeated, and washed with 10 mils water, filtrate mixed with 6.5 sodium carbonate monohydrated dissolved in 30 mils water, filtered, washed and made up to 100 mils. Freshly prepared.
Sodium Nitroprusside.	1 gram dissolved in 10 mils water. Freshly prepared.
Sodium Phosphate.	10 grams dissolved in 100 mils water.
Sodium and Potassium Tartrate. (Rochelle Salt).	10 grams dissolved in 100 mils water.
Sodium Sulphide.	10 grams dissolved in 100 mils water.
Sodium Tartrate.	10 grams dissolved in 100 mils water.
Sodium Thiosulphate.	2.5 grams dissolved in 100 mils water.
Stannous Chloride.	Pure tin boiled with hydrochloric acid conc. having metal in excess; when saturated, crystals will form, which are separated and drained and dissolved in 10 parts of water and the

	solution preserved in a well-stoppered bottle containing tin foil.
Starch.	0.5 gram starch mixed with 10 mils water and added to 90 mils boiling water.
Sulphanilic Acid.	0.5 gram dissolved in a mixture of 15 mils glacial acetic acid and 135 mils recently boiled water.
Sulphomolybdic Acid. (Froehde's Reagent).	10 grams molybdic acid or sodium molybdate dissolved in 100 mils sulphuric acid conc.
Tannic Acid.	10 grams dissolved in 10 mils alcohol and 90 mils water added.
Tartaric Acid.	10 grams dissolved in 30 mils water.
Turmeric.	Powder is digested with several portions of water which are discarded. Then treated with six times its weight of alcohol for several days and filtered.

EQUIVALENTS OF WEIGHTS AND MEASURES

From 480 Grains Down

Grains	Metric weight and measure. Gram or cm.	Minims (of Water at 4° C.)	Grains	Metric weight and measure, Gram or cm.	Minims (of Water at 4° C.)
480	31.103	504.8	240	15.552	252.4
478.4	31	503.1	231.5	15	243.5
475.4	30.805	500	228.2	14.786	240
463.0	30	486.9	218.75	14.175	230.1
456.4	29.573	480	216.1	14	227.2
450	29.160	473.3	210	13.608	220.9
447.5	29	470.7	200.6	13	211.0
437.5	28.350	460.1	199.7	12.938	210
432.1	28	454.5	185.2	12	194.8
427.9	27.725	450			
420	27.216	441.7	180	11.664	189.3
416.7	27	438.2	171.1	11.090	180
401.2	26	422.0	169.8	11	178.5
399.3	25.876	420	154.3	10	162.3
390	25.272	410.2	150	9.720	157.8
385.8	25	405.8	142.6	9.242	150
380.3	24.644	400	138.9	9	146.1
370.8	24.028	390	123.5	8	129.8
370.4	24	389.5			
360	23.328	378.6	120	7.776	126.2
354.9	23	373.3	114.1	7.393	120
342.3	22.180	360	109.37	7.087	115.0
339.5	22	357.1	108.0	7.	113.6
330	21.384	347.1	100	6.480	105.2
324.1	21	340.8	95.1	6.161	100
313.8	20.331	330	92.6	6	97.4
308.6	20	324.6	80	5.184	84.1
			77.2	5.	81.2
			76.1	4.929	80
			61.7	4	64.9
300	19.440	315.5	60	3.888	63.1
293.2	19	308.4	57.0	3.697	60
285.2	18.483	300	54.69	3.544	57.5
277.8	18	292.2	47.5	3.081	50
270	17.496	284.0	50.	3.240	52.6
262.4	17	275.9	46.3	3	48.7
256.7	16.635	270	42.8	2.772	45
246.9	16	259.7	40	2.592	42.1
			38.0	2.464	40.
			33.3	2.156	35
			30.9	2	32.5

EQUIVALENTS OF WEIGHTS AND MEASURES—*Continued*

Grains	Metric weight and measure, Gram or cm.	Minims (of Water at 4° C.)	Grains	Metric weight and measure, Gram or c.c.	Minims (of Water at 4° C.)
30	1.944	31.55	10	0.648	10.52
28.52	1.848	30	9.51	0.616	10
23.77	1.540	25	9	0.583	9.47
20	1.296	21.00	8.56	0.554	9
19.02	1.232	20	8	0.518	8.41
15.4324	1	16.23	7.71	0.5	8.12
			7.61	0.493	8
			7	0.454	7.36
			6.66	0.431	7
			6	0.389	6.31
			5.70	0.370	6
15	0.972	15.78	5	0.324	5.26
14.26	0.924	15	4.75	0.308	5
14	0.907	14.72	4	0.259	4.21
13.31	0.863	14	3.80	0.246	4
13	0.842	13.67	3	0.194	3.16
12.36	0.801	13	2.85	0.185	3
12	0.778	12.62	2	0.130	2.10
11.41	0.739	12	1.90	0.123	2
11	0.713	11.57	1	0.06480	1.0517
10.46	0.678	11	0.9508	0.06161	1

EQUIVALENT WEIGHTS AND MEASURES

From 5 Grains Down

Grams	Grains		Grams	Grains	
	In decimal fractions	In common fractions (Approximate)		In decimal fractions	In common fractions (Approximate)
0.324	5	5	0.0285	0.44	7/16
0.291	4.5	4½	0.0259	0.40	2/5
0.259	4	4	0.0246	0.38	3/8
0.227	3.5	3½	0.0201	0.31	5/16
0.194	3	3	0.0162	0.25	1/4
0.162	2.5	2½	0.0123	0.19	3/16
0.130	2	2	0.0084	0.13	1/8
0.097	1.5	1½	0.0039	0.06	1/16
0.065	1	1	0.0032	0.05	1/20
			0.0026	0.04	1/25
			0.0022	0.033	1/30
0.0609	0.94	15/16	0.0018	0.028	1/36
0.0583	0.90	9/10	0.0016	0.025	1/40
0.0570	0.88	7/8	0.0013	0.02	1/50
0.0531	0.82	13/16	0.0011	0.017	1/60
0.0518	0.80	4/5	0.0010	0.015	1/64
0.0486	0.75	3/4	0.0006	0.01	1/100
0.0447	0.69	11/16	0.0005	0.008	1/128
0.0408	0.63	5/8	0.0004	0.0065	1/160
0.0363	0.56	9/16	0.0003	0.005	1/210
0.0324	0.5	1/2	0.0002	0.003	1/320
			0.0001	0.0015	1/640

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